1b in which a p-methoxy group destabilizes the transition state.

The values of $\Delta S^{\ddagger}$ for 1 are much more negative than those observed for other nitrones (+2 to −4 eu)[26,27b,c] and the near-zero value expected for unimolecular reactions,[26] especially given the highly ordered ground state in the present case. The major factor in the magnitude of this value is probably solvent ordering due to the localized charge buildup on C_α. More specifically, there may be alignment of the acetone dipole with an increased dipole of the transition state.[26]

It is interesting to note that certain examples of three classes of compounds, oxaziridine 10,[12] imidate 2,[10] and the nitrones 1, undergo configurational isomerization at unusually enhanced rates. Significantly, all contained α-aryl, α-methoxy, and *N-tert*-butyl groups, but it is likely that they proceed by different mechanisms in each case: a ring opening for 10, N inversion[31] for 2, and bond rotation for 1.

Conclusions

Unlike most nitrones, the present *C*-methoxy-*C*-aryl-*N-tert*-butylnitrones show a marked solvent effect on isomer preference. In chloroform they exist exclusively as the *E* isomers in conformations more syn- than anti-periplanar, as shown by ^{1}H NMR and NOE difference spectra. In the more polar acetone they existed exclusively as the more polar *Z* isomers. MNDO geometry-optimized structures are consistent with conformations based on NMR results. It appears that the several steric interactions balance out in the two isomers leaving their dipole moment difference as the main factor in determining isomer preference. The unusually low $\Delta H^{\ddagger}$ values reflect ground-state strain that is relieved on bond rotation in going to the transition state. Negative $\Delta S^{\ddagger}$ values are consistent with solvent reorganization accompanying buildup of charge in the transition state.

Experimental Section

Alkylation of hydroxamic acids with methyl triflate gave the nitrone hydrotriflates as previously described,[6] and deprotonation on silica gel preparative TLC plates gave the corresponding nitrones.[6] NMR spectra were run on a 300-MHz Bruker AM300 instrument and NOE difference spectra performed as described earlier.[10] Errors for % enhancements are based on three differences of reference to enhanced signals. Off-resonance and on-resonance saturating frequencies were alternated in 8–8 pulse cycles in order to minimize effects of spectrometer instabilities,[32] and each cycle was preceded by three dummy scans to ensure a steady-state condition. This procedure is comparable to four pulse/cycle procedures.[32,33]

MO Calculations. A MOPAC program was used for MNDO calculations on Digital VAX 11/750. The starting geometry for calculations of (*Z*)-*C*-phenyl-*C*,*N*-dimethylnitrone was taken by combining structural data of (*Z*)-*S*-methyl *N*-methylthiobenzimidate *N*-oxide,[8] acetaldehyde,[34] and benzene.[34] After energy minimization, the optimized values of this nitrone were used for the initial dimensions of 1a. The phenyl twist angle was initially set to 90° (orthogonal), that of H_3C–O–C_α–C_{phenyl} to 0° (*syn*-periplanar), and that of O–N–C–O to 180° or 0° for *E* and *Z* isomers, respectively.

Kinetics. Chloroform solutions of the *E* isomers of 1a, 1b, and 1c were evaporated to dryness under a stream of dry nitrogen at 0 °C, and acetone-d_6 (MSD Isotopes) was added to give dilute solutions (concentrations <1% or 0.05 M). Rates of isomerizations were monitored by ^{1}H NMR at reduced temperature (280–265 K). Temperature was regulated by a B-VT100 temperature control unit (Bruker), factory-calibrated to an accuracy of ±0.3 K for the range used. All spectra taken during a given kinetic run were phased with the same phasing parameters. Observations were made at approximately equal time intervals that were estimated to yield at least 10 data points over the first half life of the *E* to *Z* conversion. This conversion appears to proceed to completion, since at long time periods there was no detectable amount of *E* present. Least-squares regression analysis was applied to the integrated intensities of the *N*-*t*-Bu signals of the *E* isomer for a pseudo-first order treatment.

Acknowledgment. This research was supported by an NSF Chemical Instrumentation Grant (CHE-8406088) and by an equipment grant from the W. M. Keck Foundation. We would like to thank Profs. Charles F. Hammer and Miklos Kertesz for most helpful discussions and Dr. Michael Dickman for the SCHAKAL drawings.

Registry No. 1a-*E*, 118891-54-6; 1a-*Z*, 135733-53-8; 1b-*E*, 118891-55-7; 1b-*Z*, 135733-54-9; 1c-*E*, 118891-56-8; 1c-*Z*, 135733-55-0; 1d-*Z*, 118891-58-0; 3-*Z*, 52392-70-8; 4-*Z* triflate, 135733-56-1; 7-*E* triflate, 135733-57-2; 7-*Z*, 135733-58-3.

Supplementary Material Available: MNDO-optimized geometry data for 1a-*E* and 1a-*Z* (2 pages). Ordering information is given on any current masthead page.

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Symmetry Breaking in Cyclodextrins: A Molecular Mechanics Investigation

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Received January 29, 1991

An analysis of the inherent features of cyclodextrins, void of water and crystal-lattice effects, has been undertaken with empirical force fields. It is found that these systems are not rigid and that symmetry breaking lowers the energies of these macrocycles. The highly symmetric structures portrayed in the literature are time-averaged views only.

Introduction

Cyclodextrins are cyclic oligomers of 1 → 4 linked α-D-glucose monomers. These molecules and their derivatives, as a class of compounds, have received considerable attention in this and more specialized journals for the past two decades.[1] The focus of these studies has been on the

0022-3263/91/1956-6357$02.50/0

ability of cyclodextrins to form inclusion complexes along with the uses of these macromolecules to serve as unique environments for chemical reactions.[2] More recently, cyclodextrins have been used in chromatography where, in addition to being able to separate constitutional isomers, they have been used to separate enantiomers.[3] Clearly, then, these molecules are of great interest to a wide range of scientists in many disciplines of chemistry.

The structural features of cyclodextrins have also been investigated. Most of the published work has been solid-state crystallographic analyses,[4] usually of inclusion complexes, or solution-phase spectroscopic studies, also of inclusion complexes.[5] These solution-phase studies are usually performed in an aqueous environment or involve polar organic solvents. Spectroscopic studies in solution using methods like NMR spectroscopy make measurements on relatively long time scales that give averaged structural information. X-ray and neutron diffraction studies obfuscate the inherent structural features of these molecules because of crystal-packing effects, and, perhaps more pernicious, because they contain waters of hydration that tend to distort the cyclodextrins by hydrogen bonding.[6]

In this paper, we consider the inherent structural features of cyclodextrins computationally. Relatively few theoretical studies of cyclodextrins have been reported to date.[7-9] The impetus for our study is that cyclodextrins have been used as chiral stationary phases (CSPs) in gas chromatography. These solid or crystalline cyclodextrins are difficult to use in GC and produce very inefficient separations. However, their simple O-alkylated derivatives, which are liquids, serve as remarkably efficient gas chromatographic CSPs.[10] In these CSPs the enantioselection is actually taking place in a melt or liquid phase. The work described here involves gas-phase calculations with the understanding that the results may differ somewhat when compared to the liquid phase. It is important, however, to begin examining the inherent conformational features of these molecules, and this is our first attempt at understanding the preferred shapes of these unique macrocyclic hosts.[11]

Cyclodextrins are usually considered to be highly symmetric species. This is evident from the literature where the molecules are presented as round structures or in caricature as a symmetric, truncated cone. This is a model and like all models is oversimplified. The main purpose of these models is to illustrate, in a simple way, the inclusion process, and for the purpose of teaching the uninitiated about the general characteristics of inclusion complexation, it is adequate. However, to understand enantiodifferentiation at the molecular level, this model is not adequate and a far more detailed view of the cyclodextrin is required. It is not clear whether the authors of these papers intend to convey to the reader that these molecules are inherently symmetric or whether the symmetric structure refers to a time-averaged view. The purpose of this paper is to begin addressing this issue. The question we pose is "do cyclodextrins have C_n symmetry where n = the number of glucose monomers in the macrocycle"? We report here the results of a molecular mechanics study of symmetry breaking in cyclodextrins.

Experimental Section

All calculations were done using the MM2 and AMBER force fields as implemented in MACROMODEL.[12] No cutoffs of any kind were invoked, and geometry optimization was accomplished with

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(11) A reviewer pointed out that our in vacuo simulations predict intraglucose O(2)–H···O(3) hydrogen bonds, which are very rarely observed in the crystal structure and, consequently, must be a computational artifact. The computed H···O bond lengths of the intraglucose hydrogen bonds are typically 2.4 Å, while those of the more acceptable interglucose bonds are 2.1 Å. Furthermore, hydrogen bonding is distinctly directional with a preferential O–H···O angle being linear. The computed intraglucose bond angles are typically near 109° while the interglucose angles are near 160°. This means the intraglucose hydrogen bonds are less stable than the interglucose bonds. Our view, however, is that relying on crystal structures of cyclodextrins, which form columnar stacks surrounded by clathrates of water to which they hydrogen bond, is especially misleading. Throughout this paper there are structures that have not yet been observed (or may not be able to exist) in the solid and, from a crystallographer's point of view, appear counterintuitive because they have no intermolecular hydrogen bonds. These structures, however, are fully consistent with chemical intuition and theoretical prediction described herein.

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the block diagonal Newton–Raphson procedure. All energies reported have a root mean square (rms) gradient of 0.2 kJ/Å mol or less for a dielectric constant of 1.5.

Cyclodextrins are comprised of glucose monomers where it was first observed that electron-withdrawing groups on the C1 carbon prefer to exist in an axial rather than equatorial conformation. This is the anomeric effect that has been exhaustively studied and is well documented.[13] Two questions need to be addressed here. First, do empirical force fields account for the anomeric effect and, second, does MACROMODEL's version of MM2 adequately reflect the original MM2 force field in this regard?

Traditional explanations of the anomeric effect invoke $\sigma-\pi^*$ orbital mixings that are not routinely accounted for in molecular mechanics. Allinger, however, has modified the MM2 force field to account for axial preference and for the fact that the C–O bond lengths are torsion angle dependent.[14] Rather than add a torsion–stretch cross-term to his valence force field, Allinger opted to adjust ℓ_0, the standard bond length, as a function of the two torsion angles involved in the C–O–C–O–C fragment. With suitable parameters a molecular mechanics treatment of the anomeric effect was achieved.

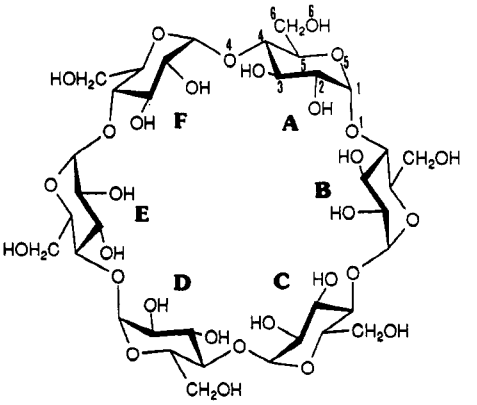
The MM2 force field in MACROMODEL is not the same as Allinger's version.[12] However, MACROMODEL does implement Allinger's changes to the original MM2 force field and it too handles the anomeric effect. A large number of test systems were run with MACROMODEL to test this, several of which are described here. First, dimethoxymethane was considered. Three conformations exist: anti, anti; anti, gauche; gauche (+), gauche (+). The MM2-82 relative energies (kcal mol^{-1}) are as follows: aa = 0.00, ag = 1.98, g^+g^+ = 4.03. MACROMODEL's relative energies are as follows: aa = 0.00, ag = 1.60, g^+g^+ = 3.0. MACROMODEL tends to underestimate MM2-82 energy differences, but there are no experimental values available for comparison in this case. However, axial 2-methoxytetrahydropyran is experimentally 1.05 kcal mol^{-1} more stable than its equatorial form and MM2-82 overestimates this. MM2-82 computes the equatorial (anti, gauche) form to be 1.17 kcal mol^{-1} less stable, while MACROMODEL predicts it to be 0.60 kcal mol^{-1} less stable. Overall, though, MACROMODEL gives the same energy trends as MM2-82. The structural changes predicted by MACROMODEL are also consistent with MM2-82. For example, in Table III of Allinger's original paper[14] the average CH_3–O bond length for the three conformations of dimethoxymethane is 1.419 Å and the average bond length for O–CH_2 is 1.402 Å. MACROMODEL's values are 1.417 and 1.407 Å, respectively. Hence, MACROMODEL, like MM2-82, correctly predicts the preferred conformations and the expected bond shortenings found in the anomeric effect.

α-, β-, and γ-Cyclodextrin structures were built and energy minimized constraining the systems to 6-, 7- and 8-fold symmetry. These constraints were removed and the system was allowed to fully relax into C_n symmetric structures where n = the number of glucose monomers in the ring. Symmetry breaking was accomplished by forcing the primary OH atoms and/or the acetal linker oxygens to fixed distances, beginning from the C_n symmetrical structures. A harmonic constraining force constant of 11 mdyn Å^{-1} was used. This slowly brings the molecule into a new equilibrium conformation as all other degrees of freedom are relaxed. This way new starting structures were generated for energy minimization.

The reader should note that this study does not represent an analysis of the distribution of conformational states accessible to the CD macrocycle. It will be shown later that these ring systems are far more flexible than previously believed, and a search for all possible conformations is untenable. Rather, we provide selected structures with different symmetries to see if there are any generalizations that can be made concerning the structures of these macrocyclic host molecules. Additionally, we point out that the structures used in this study are minima but the nature of these minima have not been thoroughly explored. The depths of some energy wells may be such that "jiggling" the atoms followed by reoptimization may give new structures and, consequently, some structures may correspond to metastable states. Finally, it will be seen that depending on the force field implemented, several structures collapse to different structures beginning from the same starting structure. In those cases, different optimizers were used to see if our results were dependent on the minimization method. We conclude that the different structures are not dependent on the minimizer, but rather on the force field.

Results and Discussion

The nomenclature and numbering scheme for the cyclodextrins studied here are presented below. Each monomer in the polymer uses the glucose atom labels depicted. Each monomer in the polymer is further designated by capital letters. α-Cyclodextrin thus has glucose atom labels for monomers A–F, β-cyclodextrin has glucose atom labels for units A–G and γ-cyclodextrin for glucose units A–H. Key torsion angles are ω = O_5–C_5–C_6–O_6 (of which there are 6, 7, and 8 for α-, β-, and γ-CD, respectively) and θ, the torsion angle formed by the glycosidic O_4 oxygen atoms linking the glucose moieties. Torsion angle ω defines the relative orientation of primary hydroxyl groups, while θ is a measure of macromolecular ring puckering ascribed to the torus as a whole. Generally speaking, the glucose moieties retained their $^4C_1$ structures and the exocyclic secondary hydroxyls retained their network of hydrogen bonding (vide infra).



Before considering the shapes these macrocycles can adopt, we point out that the work to be discussed is based on empirical force fields and, accordingly, the results derived herein can be only as good as the force field itself. The MM2 force field can calculate structural features for a variety of organic functional groups within experimental error. The computed heats of formation has a standard deviation of 0.42 kcal mol^{-1}, which improves to 0.37 kcal mol^{-1} when vibrational effects are included.[15] The original MM2 force field, however, has a significant number of documented inadequancies[16] including the way it treated hydrogen bonds (a key point in the work described here). Allinger recognized this and modified MM2 to better treat hydrogen bonding.[17] During parameterization he focused on the methanol dimer where two forms are important: a cyclic dimer and a more stable linear dimer. Allinger took special care to ensure that the linear form be more stable than the cyclic form and that the dimerization energy and oxygen–oxygen distance (MM2-87 2.779 Å) be in agreement with experimental and quantum mechanical values. MACROMODEL's version of MM2 likewise gives reasonable

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Table I. Energies (kcal mol^{-1}), Symmetries, and Torsion Angles of C_n Normal Cyclodextrins

α-cyclodextrin (1) MM2 E = −135.3 C_6 AMBER E = 16.0 C_6 torsion angles (deg) (MM2/AMBER)		β-cyclodextrin (2) MM2 E = −158.8 C_7 AMBER E = 4.4 C_1[a] torsion angles (deg) (MM2)		γ-cyclodextrin (3) MM2 E = −185.0 C_8 AMBER E = 1.1 C_1[a] torsion angles (deg) (MM2)	
ω_A = −60/−46	θ_A = 0/0	ω_A = −62	θ_A = −1	ω_A = −62	θ_A = 1
ω_B = −60/−46	θ_B = 0/0	ω_B = −61	θ_B = 2	ω_B = −62	θ_B = −2
ω_C = −60/−46	θ_C = 0/0	ω_C = −62	θ_C = −2	ω_C = −61	θ_C = 0
ω_D = −60/−46	θ_D = 0/0	ω_D = −61	θ_D = 0	ω_D = −62	θ_D = 1
ω_E = −60/−46	θ_E = 0/0	ω_E = −62	θ_E = 1	ω_E = −62	θ_E = 1
ω_F = −60/−46	θ_F = 0/0	ω_F = −61	θ_F = 0	ω_F = −61	θ_F = 3
		ω_G = −62	θ_G = 0	ω_G = −62	θ_G = −3
				ω_H = −61	θ_H = 3

[a] Structure reverts to C_1 symmetry.

Table II. Energies (kcal mol^{-1}), Symmetries, and Torsion Angles for Symmetric Open Cyclodextrins

α-cyclodextrin (4) C_6 MM2 E = −127.5 AMBER E = 36.1 torsion angles (deg) (MM2/AMBER)		β-cyclodextrin (5) C_7 MM2 E = −150.5 AMBER E = 34.8 torsion angles (deg) (MM2/AMBER)		γ-cyclodextrin (3) C_8 MM2 E = −175.9 AMBER E = 40.9 torsion angles (deg) (MM2/AMBER)	
ω_A = 63/60	θ_A = 0/0	ω_A = 61/59	θ_A = −1/−1	ω_A = 59/58	θ_A = 0/1
ω_B = 63/60	θ_B = 0/0	ω_B = 62/60	θ_B = 2/2	ω_B = 60/59	θ_B = −1/−1
ω_C = 63/60	θ_C = 0/0	ω_C = 61/59	θ_C = −1/−1	ω_C = 60/59	θ_C = −1/−1
ω_D = 63/60	θ_D = 0/0	ω_D = 62/60	θ_D = 1/0	ω_D = 60/59	θ_D = 0/0
ω_E = 63/60	θ_E = 0/0	ω_E = 61/59	θ_E = 0/0	ω_E = 60/59	θ_E = 1/0
ω_F = 63/60	θ_F = 0/0	ω_F = 62/59	θ_F = 1/0	ω_F = 60/59	θ_F = 0/1
		ω_G = 61/59	θ_G = −1/0	ω_G = 60/58	θ_G = −2/−3
				ω_H = 60/59	θ_H = 2/2

Table III. Energies (kcal mol^{-1}), Symmetries, and Torsion Angles of Symmetric Closed Cyclodextrins

α-cyclodextrin (7) C_6 MM2 E = −133.7 AMBER E = 32.2 torsion angles (deg) (MM2/AMBER)		β-cyclodextrin (5) C_7 MM2 E = −153.2 AMBER E = 40.4 torsion angles (deg) (MM2/AMBER)		γ-cyclodextrin (3) C_8 MM2 E = −83.0 AMBER E[a] torsion angles[a] (deg) (MM2)	
ω_A = 95/96	θ_A = 0/0	ω_A = 101/101	θ_A = 0/−1	ω_A = 76	θ_A = 2
ω_B = 95/96	θ_B = 0/0	ω_B = 99/100	θ_B = 1/2	ω_B = 74	θ_B = 0
ω_C = 95/96	θ_C = 0/0	ω_C = 102/102	θ_C = −1/−1	ω_C = 73	θ_C = −2
ω_D = 95/96	θ_D = 0/0	ω_D = 98/99	θ_D = 0/0	ω_D = 74	θ_D = 1
ω_E = 95/96	θ_E = 0/0	ω_E = 101/102	θ_E = 0/0	ω_E = 75	θ_E = 1
ω_F = 95/96	θ_F = 0/0	ω_F = 100/100	θ_F = 0/0	ω_F = 74	θ_F = 0
		ω_G = 100/100	θ_G = 0/0	ω_G = 74	θ_G = −1
				ω_H = 74	θ_H = 0

[a] No AMBER structure exists

results for alcohols. The O–O distance in the linear dimer is 2.792 Å (2.766 Å AMBER) and the O–H···O angle of 160° (171° AMBER) is tolerable for our work. In contrast, the linear water dimer has an unrealistic MM2 O–O distance of 2.619 Å and an O–H···O angle of 129°. Evidently, the carbon–oxygen bond moments and/or dispersion forces found in alcohols (but missing in water) accounts for the reliable hydrogen bonding in alcohols. The quality of the MM2 force field is thus inadequate for water but reasonable for alcohols. Furthermore, the agreement between MM2 and AMBER structures is reasonable; the superposition of MM2-optimized α-D-glucose with AMBER-minimized α-D-glucose has an rms deviation of only 0.081 Å for all atoms. Some skepticism, however, should be borne in mind when considering our results especially when there are disagreements between MM2 and AMBER. An especially good discussion of why hydrogen bonding is a difficult problem in the molecular modeling of carbohydrates is provided by Jeffrey.[18]

I. Normal Cyclodextrins. Several C_n starting structures differing in torsion angle ω were considered. This torsion angle is the torsion angle formed by O_5–C_5–C_6–O_6 and can adopt three orientations: g^- (−60°), g^+ (+60°) and t (180°). The latter orientation is rarely observed, gave very high computed energies, and consequently was not further considered. It has been noted that cyclodextrins prefer the g^- conformation (g^+ can exist if guest molecules can hydrogen bond), and so this structure was initially used.[19] The C_n structures with g^- primary OH orientations are shown in Figure 1. Relevant torsion angles and energies are listed in Table I. It is to be noted that while MM2 located C_n symmetric structures, AMBER could not find g^- C_7 and C_8 conformations for β- and γ-cyclodextrins, respectively. Rather, low-energy distorted shapes evolved (vide infra). From these shapes it became apparent that gross structural reorganizations can take place in cyclodextrins. One structural type has the primary OH groups directed inward, so we call these "in" structures. The other type has the primary OH groups canted outward and are

(18) Jeffrey, G. A. In *Computer Modeling of Carbohydrate Molecules*; ACS Symposium Series 430; French, A. D., Brady, J. W., Eds.; American Chemical Society: Washington, DC, 1990; Chapter 2.

(19) Saenger, W. *Biochem. Soc. Trans.* **1983**, *11*, 136.

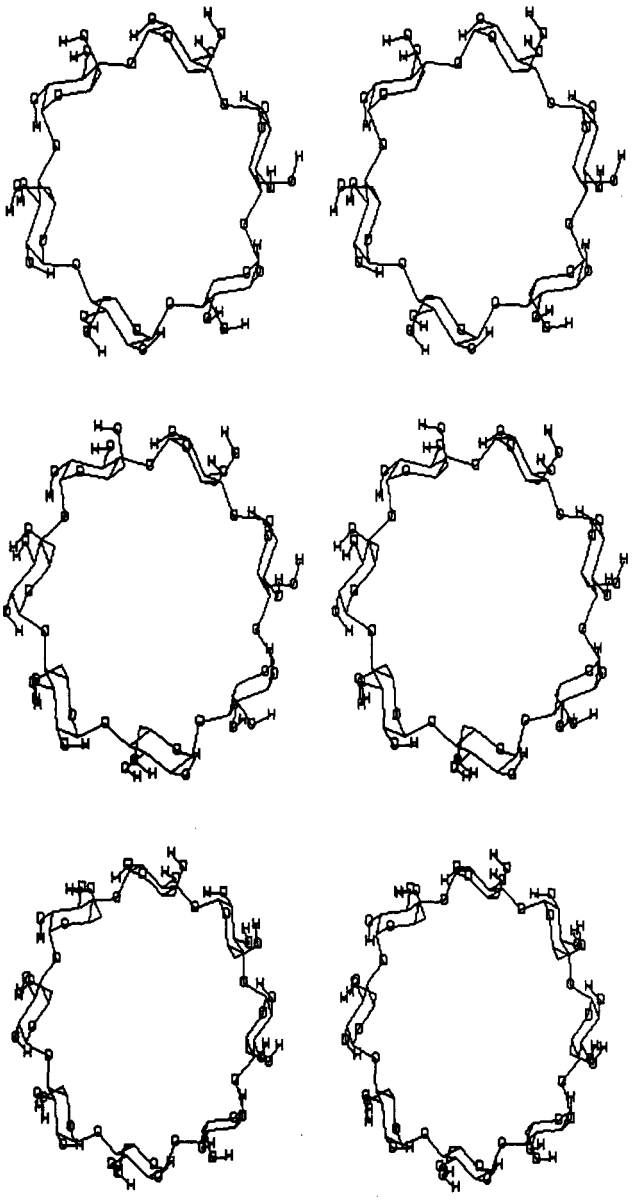

Figure 1. Stereographic views of MM2-minimized cyclodextrins: top, α-cyclodextrin 1; middle, β-cyclodextrin 2: bottom, γ-cyclodextrin 3. Views are from the primary hydroxyl rim. C_n (where n = number of glucose monomers) symmetry exists.

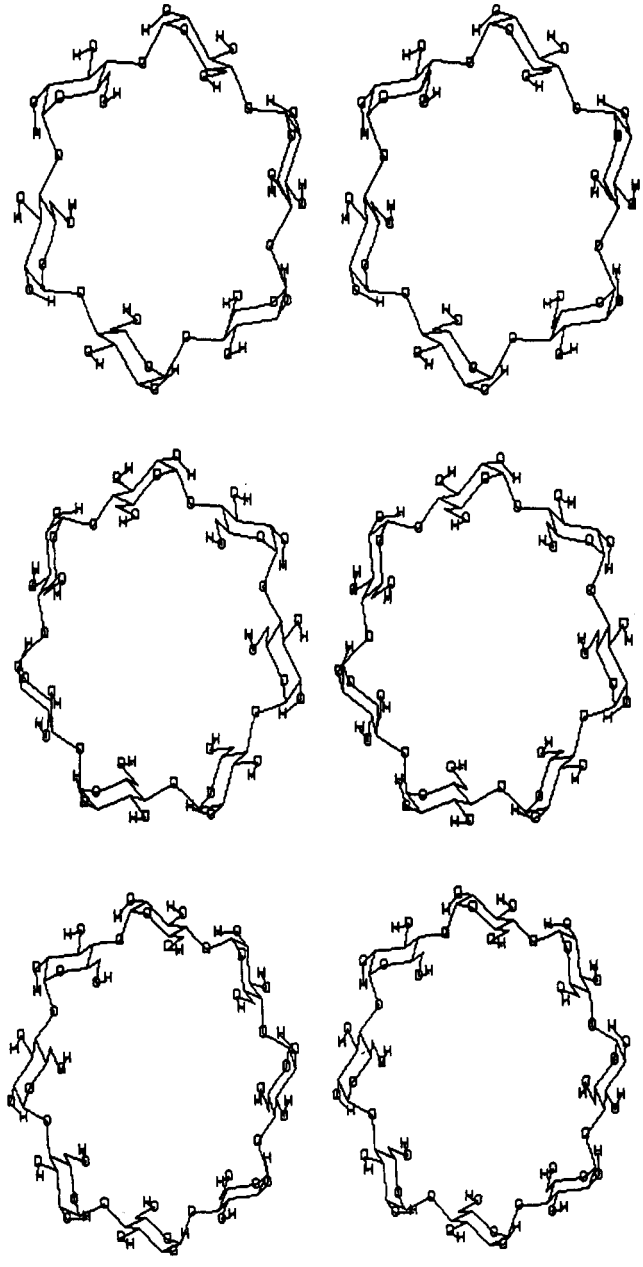

Figure 2. Stereographic views of MM2-minimized "in" cyclodextrins with open orifices: top, α-cyclodextrin 4; middle, β-cyclodextrin 5; bottom, γ-cyclodextrrin 6. Views are from the primary hydroxyl rim.

called "out" structures. We now consider these abnormal conformations.

II. In Structures. A. C_n Symmetry. The normal, guest-free cyclodextrin generally assumes the g^- conformation in the solid state.[19] Beginning with g^+ shapes we were able to find lower energy C_n symmetric conformers of cyclodextrins. These structures are shown in Figure 2. Relevant torsion angles and energies are listed in Table II.

Another set of g^+, C_n cyclodextrins also exist. They are shown in Figure 3 and differ from their counterparts in Figure 2 by having their torison angles ω rotated from 60° to 100°. The energies and selected torsion angles of these highly symmetric structures are presented in Table III.

The rotation of ω from 60° to 100° results in a closing of the bottom rim of the cyclodextrin, much like the iris of an optics system. When the torsion angles are ~100° a network of interglucose primary OH bonds forms as shown in Figure 3. Because the bottom rim is closed we refer to this as the "closed" form. Similarly, when ω = 60° a network of intraglucose hydrogen bonding arises and, since the bottom rim is opened, we refer to these structures as "opened" forms. The size differential of the open and closed forms is clearly visible in the figures.

The relative energies of the open and closed forms are interesting. Both MM2 and AMBER indicate the closed form of α-CD to be most stable. For β-CD, however, MM2 predicts the closed form to be approximately 3 kcal mol^{-1} more stable while AMBER predicts the open form to be more stable by about 5 kcal mol^{-1}. Finally, for γ-CD, only the open form is predicted to exist. Indeed, the MM2 closed structure shown in Figure 3 is a metastable state that, with a minor perturbation, rapidly converges to the open form. Furthermore, using AMBER, this metastable state can not be located if it exists at all.

The trend is clear, as the size of the oligomer increases, the ability to form a stabilizing network of primary OH groups is lost. The diameter of the circle formed by the acetal linker oxygens in α-CD is ~8.5 Å, the diameter in β-CD is ~9.9 Å, and for γ-CD it is 11.6 Å. Clearly, for

Table IV. Energies (kcal mol^{-1}), Symmetries, and Torsion Angles of α-Cyclodextrin Conformers 10–12

conformer 10 C_3 MM2 E = −139.0 AMBER E = 22.1 (torsion angles (deg) (MM2/AMBER)		conformer 11 C_2 MM2 E = −137.8 AMBER E = 20.4 torsion angles (deg) (MM2/AMBER)		conformer 12 C_2 MM2 E = −138.3 AMBER E = 19.2 torsion angles (deg) (MM2/AMBER)	
ω_A = 58/57	θ_A = −12/−24	ω_A = 84/76	θ_A = 0/22	ω_A = 94/82	θ_A = 23/23
ω_B = 88/84	θ_B = 12/24	ω_B = 59/59	θ_B = −4/4	ω_B = 93/84	θ_B = −17/3
ω_C = 58/57	θ_C = −12/−24	ω_C = 122/163	θ_C = 2/−21	ω_C = 76/46	θ_C = −9/−29
ω_D = 88/84	θ_D = 12/24	ω_D = 84/76	θ_D = 1/22	ω_D = 92/85	θ_D = 23/21
ω_E = 58/57	θ_E = −12/−24	ω_E = 60/58	θ_E = −4/4	ω_E = 88/83	θ_E = −17/8
ω_F = 88/84	θ_F = 12/24	ω_F = 121/163	θ_F = 2/−21	ω_F = 78/58	θ_F = −9/−33

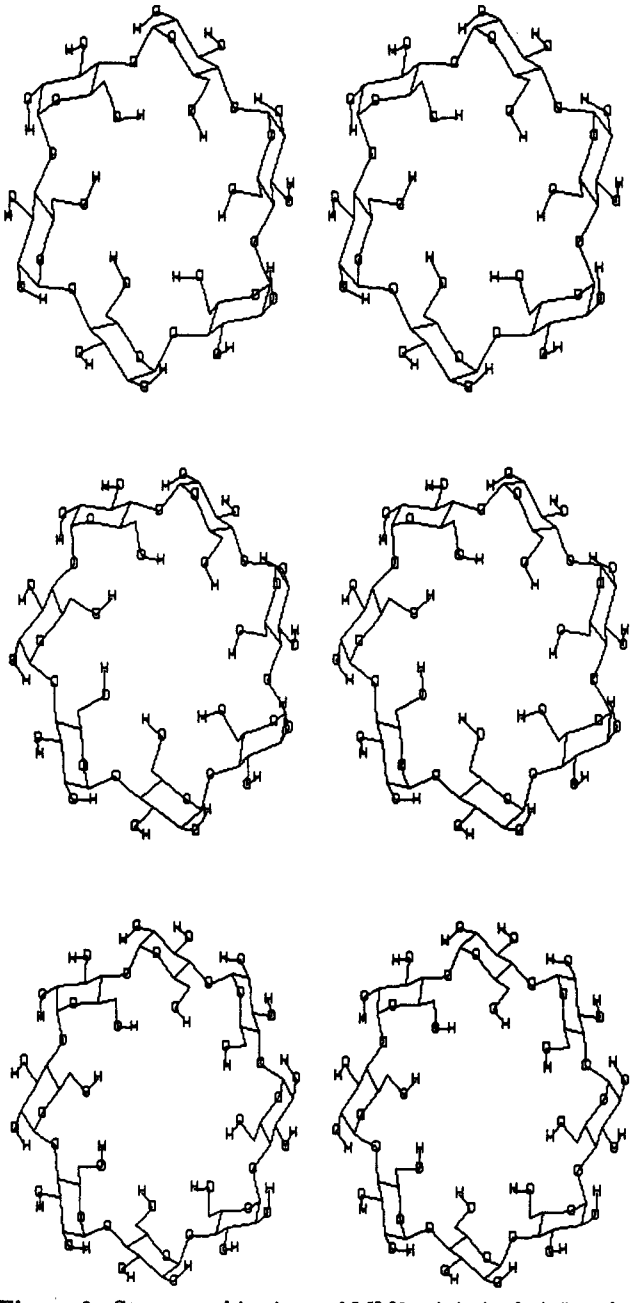

Figure 3. Stereographic views of MM2-minimized "in" cyclodextrins with closed orifices: top, α-cyclodextrin **7**; middle, β-cyclodextrin **8**; bottom, γ-cyclodextrin **9**. Views are from the primary hydroxyl rim.

α-CD the glucose units with their pendant primary OH groups can easily reach one another to form this network but in γ-CD the glucose units are too far apart. The cross-over point for cyclodextrins having the ability to exist in a symmetrical closed form appears to be the 7 unit β-cyclodextrin.

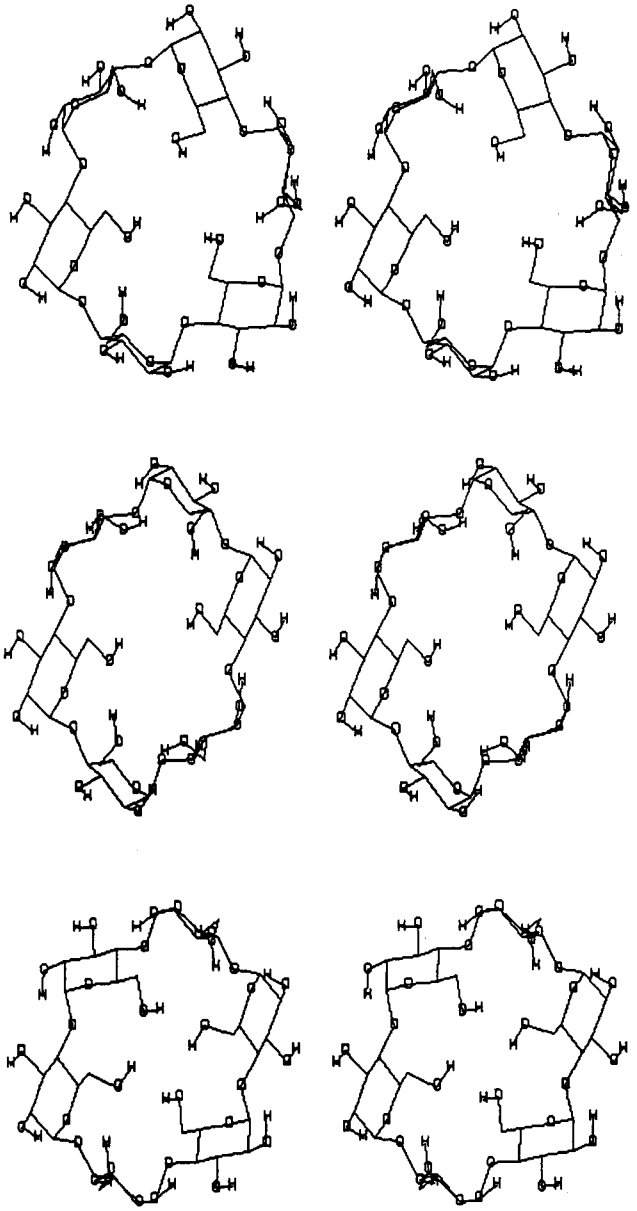

Figure 4. Stereographic views of α-cyclodextrin with low symmetry: top, "in" α-cyclodextrin **10** with C_3 symmetry; middle, "in" α-cyclodextrin **11** with C_2 symmetry; bottom, "in" α-cyclodextrin **12** with C_2 symmetry.

B. Lower Symmetry. 1. α-Cyclodextrin. The aim of this work is to examine whether or not cyclodextrins with the highest symmetry allowed are the most stable conformations. For α-cyclodextrin with 6-fold symmetry we examined what happens when the system adopts 3-fold symmetry and then 2-fold symmetry. The C_3 α-cyclodextrin, **10**, is presented in stereo in Figure 4. Also included in this figure are two low-energy C_2 structures **11** and **12**. The MM2 and AMBER energies along with

Table V. Energies (kcal mol^{-1}), Symmetries, and Torsion Angles of β-Cyclodextrin Conformers 13-14

conformer 13 C_1 MM2 E = −160.9 AMBER E = 26.3 torsion angles (deg) (MM2/AMBER)		conformer 14 C_1 MM2 E = −164.3 AMBER E = 24.8 torsion angles (deg) (MM2/AMBER)	
ω_A = 61/81	θ_A = −8/−4	ω_A = 75/76	θ_A = 31/33
ω_B = 136/150	θ_B = −3/−7	ω_B = 52/52	θ_B = −19/−21
ω_C = 100/82	θ_C = 18/36	ω_C = 151/158	θ_C = −10/−15
ω_D = 58/49	θ_D = −11/−29	ω_D = 91/92	θ_D = 7/9
ω_E = 157/157	θ_E = −8/−7	ω_E = 150/146	θ_E = 13/28
ω_F = 77/75	θ_F = 11/16	ω_F = 57/57	θ_F = −13/−31
ω_G = 58/53	θ_G = 1/−6	ω_G = 162/157	θ_G = −14/−12

pertinent torsion angles are presented in Table IV.

It is found that all three structures have similar energies and will be populated at room temperature. We point out here that the energies reported are simple steric energies, not free energies, and one can anticipate substantial entropy of mixing to influence the distribution of conformational states. Counterbalancing this, of course, will be the entropy of symmetry number. The key point is that all conformations are of lower energy than any 6-fold symmetric conformation described earlier.

The structural features of these conformations are quite interesting and, heretofore, not yet noted. The C_3 α-cyclodextrin has glucose units rolled into or out of the cavity in alternating fashion. This allows for a network of hydrogen bonding on the lower rim. Those primary hydroxyls contributing to this interglucose hydrogen bonding network look like those of the closed α-CD described above (ω ~88°), while the other primary hydroxyls look like the open form of the 6-fold symmetric structure (ω ~57°). To adopt this structure the macromolecule as a whole buckles. The torsion angles θ, describing the planarity of the equatorial acetal linker oxygens, alternates ±11° (±24° AMBER).

Of the two conformers with 2-fold symmetry one finds this belt of acetal oxygens nearly planar in one case (11), while in the other (12) it is severely puckered (see θ in Table IV). Conformer 12 has a network of four primary hydrogen bonds and is slightly more stable than the other C_2 conformer. Although other structures of comparable energy with less than C_6 symmetry probably exist (an exhaustive search was not carried out), the results here indicate that the round, highly symmetric structure of α-cyclodextrin is not inherently the most stable conformation.

2. β-Cyclodextrin. Unlike α- and γ-cyclodextrin with an even number of glucose monomers, the β-cyclodextrin has an odd number of units. Symmetry breaking can give only C_1 structures. It was not clear how to generate these low-energy conformers. One approach was to constrain four of the seven primary hydroxyls (from glucose units B, D, F, and G) into a closed form where a network of four interglucose hydrogen bonds would result. Three of the seven primary hydroxyls (those from glucose units A, C, and E) were simultaneously constrained into an open form. Beginning with these constraints the system was allowed to fully relax. The final structure had C_1 symmetry with a high steric energy (MM2 = −154 kcal mol^{-1}) and was not considered further. Another symmetry breaking attempt was to place the primary hydroxyls of glucose units A, C, and E into a closed form, with glucose hydroxyls from B, D, F, and G into an open form, hoping that a pseudo-3-fold symmetric hydrogen bonding scheme, as found in **10**, would result. Relaxation from this structure likewise resulted in a nonsymmetric conformation of high energy.

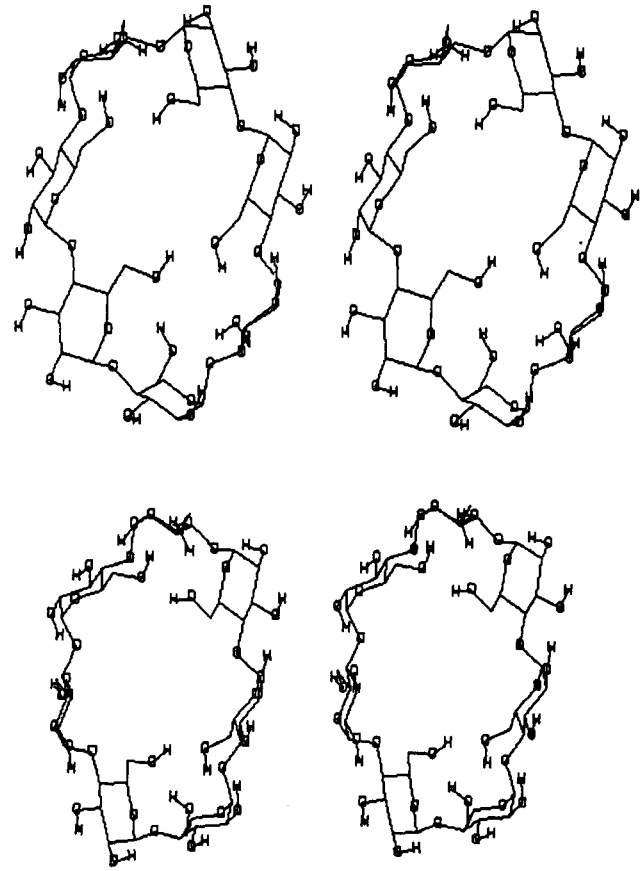

Figure 5. Stereographic views of "in" β-cyclodextrins with C_1 symmetry. The views are from the primary hydroxyl rim to highlight the networks of hydrogen bonding that are possible: top β-cyclodextrin **14**; bottom, β-cyclodextrin **13**.

During our attempts to generate conformations of lower symmetry we noted the propensity for the primary hydroxyls to form small clusters (dimers, trimers, tetramers) of hydrogen-bonded OH's on the lower rim of the cyclodextrins.[20] Two of these low-energy conformations are shown in Figure 5, and their energies and torsion angles are listed in Table V. Both structures **13** and **14** have pseudo, 2-fold mirror symmetry. In **14**, a trimer of primary hydroxyl groups from glucose units B–D exists, a trimer of primary hydroxyl groups from glucose units E–G exists (as distinct clusters), and a single glucose hydroxyl, from monomer A, is intramolecularly hydrogen bonded. For conformer **13**, a trimer of hydrogen-bonding primary hydroxyls exists (involving glucose units A, B, and G) and a tetrameter exists (involving glucose units C–F). This latter structure is the most stable conformation located, again suggesting that β-cyclodextrin with C_7 symmetry is not the most stable shape. This has been noted before by Sato's group[8j] but not elaborated upon. The hydrogen bond H---O distances in **13** are between 2.0 and 2.3 Å and those in **14** are between 1.8 and 1.9 Å. Overall, the propensity for β-cyclodextrin to form clusters or pools of primary OH hydrogen bonds is noted. This clustering tends to maximize hydrogen bonding cooperativity.[20] To do this, the system tends to buckle somewhat (see θ values in Table V). Again, other low-energy structures may exist but exhaustive conformational searches were not performed; we only wish to illustrate here that the highly symmetric structures inferred from the literature are not the most

(20) Cooperative effects in extended hydrogen-bonding systems in cyclodextrins are well studied: Koehler, J. E. H.; Saenger, W.; Lesyng, B. *J. Comput. Chem.* **1987**, *8*(8), 1090.

Table VI. Energies (kcal mol^{-1}), Symmetries, and Torsion Angles of γ-Cyclodextrin Conformers 15–17

conformer 15 C_4 MM2 E = −190.4 AMBER E = 25.9 torsion angles (deg) (MM2/AMBER)		conformer 16 C_2 MM2 E = −190.0 AMBER E = 13.6 torsion angles (deg) (MM2/AMBER)		conformer 17 C_2 MM2 E = −190.3 AMBER E = 28.4 torsion angles (deg) (MM2/AMBER)	
ω_A = 59/63	θ_A = 12/24	ω_A = 74/77	θ_A = 56/72	ω_A = 94/87	θ_A = 25/38
ω_B = 131/164	θ_B = −12/−24	ω_B = 55/55	θ_B = −36/−21	ω_B = 58/56	θ_B = −45/−64
ω_C = 59/63	θ_C = 12/24	ω_C = 61/64	θ_C = −2/−21	ω_C = 156/163	θ_C = −1/−4
ω_D = 131/164	θ_D = −12/−24	ω_D = 163/167	θ_D = −20/−36	ω_D = 90/95	θ_D = 11/14
ω_E = 59/63	θ_E = 12/24	ω_E = 75/77	θ_E = 55/77	ω_E = 94/87	θ_E = 25/38
ω_F = 131/164	θ_F = −12/−24	ω_F = 56/58	θ_F = −32/−26	ω_F = 58/56	θ_F = −45/−64
ω_G = 59/63	θ_G = 12/24	ω_G = 58/47	θ_G = 9/−20	ω_G = 159/163	θ_G = −1/−4
ω_H = 131/164	θ_H = −12/−24	ω_H = 163/172	θ_H = −14/−34	ω_H = 90/95	θ_H = 11/14

Table VII. Energies (kcal mol^{-1}), Symmetries, and Torsion Angles of Out Cyclodextrin Conformers

α-cyclodextrin (18) C_3 MM2 E = −135.4 AMBER E = 8.6 torsion angles (deg) (MM2/AMBER)		β-cyclodextrin (20) C_1 MM2 E = −163.5 AMBER E = 2.9 torsion angles (deg) (MM2/AMBER)		γ-cyclodextrin (21) C_4 MM2 E = −192.8 AMBER E = −0.10 torsion angles (deg) (MM2/AMBER)	
ω_A = −59/−48	θ_A = −8/−14	ω_A = −60/−52	θ_A = −7/−16	ω_A = −60/−50	θ_A = −14/−22
ω_B = −55/−44	θ_B = 8/14	ω_B = −55/46	θ_B = 13/20	ω_B = −55/−44	θ_B = 15/25
ω_C = −59/−48	θ_C = −8/−14	ω_C = −60/−49	θ_C = −11/−16	ω_C = −60/−50	θ_C = −15/−26
ω_D = −55/−44	θ_D = 8/14	ω_D = 57/46	θ_D = −1/5	ω_D = −55/−44	θ_D = 14/23
ω_E = −59/−48	θ_E = −8/−14	ω_E = −60/−48	θ_E = −11/7	ω_E = −60/−50	θ_E = −14/−22
ω_F = −55/−44	θ_F = 8/14	ω_F = −60/−49	θ_F = −11/−14	ω_F = −55/−44	θ_F = 15/25
		ω_G = 56/−49	θ_G = 6/14	ω_G = −60/−50	θ_G = −15/−26
				ω_H = −55/−44	θ_H = 14/23

α-cyclodextrin (19) C_2 MM2 E = −135.6 AMBER E = 7.7 torsion angles (deg) (MM2/AMBER)		γ-cyclodextrin (22) C_2 MM2 E = −193.6 kcal mol^{-1} AMBER E[a] torsion angles (deg) (MM2)	
ω_A = −59/−48	θ_A = 9/13	ω_A = −60	θ_A = −18
ω_B = −59/−48	θ_B = −4/−12	ω_B = 56	θ_B = 20
ω_C = −56/−45	θ_C = −5/−1	ω_C = −56	θ_C = −14
ω_D = −59/−48	θ_D = 9/13	ω_D = −56	θ_D = 12
ω_E = −59/−48	θ_E = −4/−12	ω_E = −61	θ_E = −18
ω_F = −56/−45	θ_F = 9/−1	ω_F = 56	θ_F = 21
		ω_G = −61	θ_G = −14
		ω_H = −56	θ_H = 12

[a] No AMBER structure exists.

stable ones, although they probably represent a time-average picture of the macromolecular ring geometry.

3. γ-Cyclodextrin. The γ-cyclodextrin was first reduced to C_4 symmetry by initially constraining every other primary OH to hydrogen bond to its neighbor. This structure, upon full relaxation, minimized to a C_4 symmetric structure **15**. This structure has torsion angles ω alternating between ~60° (63° AMBER) and 130° (164° AMBER). Torsion angle θ alternates ±12° (±24° AMBER), showing a significant puckering into a 4-fold crownlike conformation. This structure is presented in Figure 6 and its energies and pertinent torsion angles are listed in Table VI.

Next, we attempted to constrain γ-cyclodextrin to C_2 symmetry by pulling together diagonal primary OH groups. Two low-energy structures with near-C_2 symmetry were located, both having energy comparable to the C_4 structure. These structures, **16** and **17**, are presented in Figure 6, and their energies and torsion angles are listed in Table VI. Again, these latter structures demonstrate severe puckering of acetal linker oxygens and, as in other flattened cyclodextrins, there are clusters of primary hydroxyl groups hydrogen bonding on the lower rim of the cyclodextrin. In conformer **16** there are two clusters of trimer hydrogen bonds and one dimer. The trimer clusters are at the ends of the oblong, flattened torus, and the dimer is a transannular hydrogen bond. In conformation **17** there appears to be two tetrameric clusters of hydrogen-bonded primary hydroxyl groups. Other near-C_2 symmetric structures of low energy also exist. Again, we point out that, as in the α- and β-cyclodextrin cases, the structure with the highest attainable symmetry is not the inherently most stable conformation.

III. Out Structures. C_n symmetric structures for α-, β-, and γ-cyclodextrins with their primary OH groups canted away from the interior of the macrocyclic cavity could not be found. However, C_3 and C_2 structures for α-cyclodextrin, C_4 and C_2 structures for γ-cyclodextrin, and C_1 structures for β-cyclodextrin do exist.

1. α-Cyclodextrin. Low-energy conformations with C_3 (**18**) and C_2 (**19**) symmetry for α-cyclodextrin were found and are presented in Figure 7. Their energies and pertinent torsion angles are listed in Table VII. While the lowest energy structure found for α-cyclodextrin is the C_3 in structure **10** according to MM2, AMBER finds the C_3 out structure **18** to be of lowest energy. Evident in Figure 7, as is found in all other figures, is the network of hydrogen bonding between the secondary OH groups. What appears to be happening is that the macromolecule is inverting so that the secondary OH rim closes down as the primary OH rim opens up. This inversion about the equatorial belt of acetal oxygen enhances hydrogen bonding in the secondary OH network at the expense of the primary OH network. While this finding is true for AMBER, it is not true for MM2 where the in primary OH network seems more stable. Given the deficiencies of the

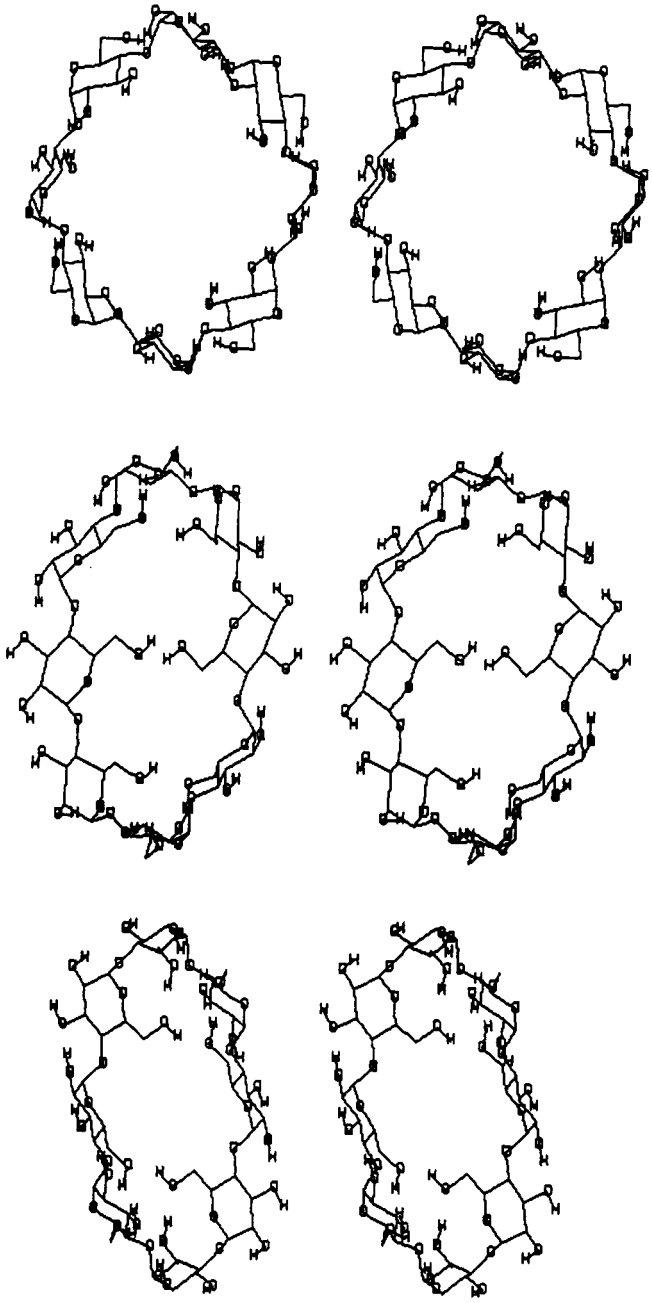

Figure 6. Stereographic views of "in" γ-cyclodextrins with lower than C_8 symmetry: top, γ-cyclodextrin **15** with C_4 symmetry; middle, γ-cyclodextrin **16** with C_2 symmetry; bottom, γ-cyclodextrin **17** with C_2 symmetry. The view is from the primary hydroxyl rim for all but **17**. This view is from the secondary hydroxyl rim to illustrate how the depth of the cavity has been decreased.

MM2 force field[16] with regard to hydrogen bonding, it is perhaps reasonable to side with AMBER in this case.

Throughout this study we encountered a force field problem. In many cases the MM2 and AMBER force fields give no regular trends (compare **1** with **10** and **2** with **14**). It would seem appropriate to examine the component energies, e.g., stretch, bend, torsion, etc. terms, and determine which force field is more appropriate. This, however, should not be done. The component energies are themselves meaningless. They reflect more what the author of the force field deemed important to reproduce his databank of experimental information, or, more likely, the component energy terms reflect the authors' parameterizations, most of which make up for the inadequacies of these valence force fields. Only the total energy (when compared to other conformer energies) has meaning. Nonetheless, we provide the component energies of each structure described in this paper as supplemental material.

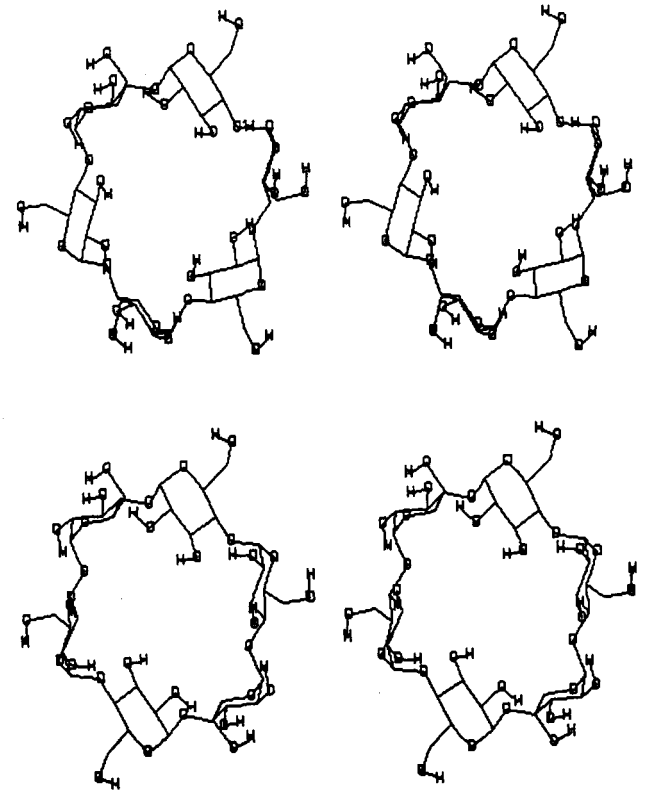

Figure 7. Stereographic views of "out" α-cyclodextrins: top, α-cyclodextrin **18** with C_3 symmetry; bottom, α-cyclodextrin **19** with C_2 symmetry. Views are from the primary hydroxyl direction illustrating how opened this orifice has become.

In a recent molecular mechanics investigation of molecular recognition by cyclodextrin mimics of α-chymotrypsin, Venanzi's group found that the addition of an *N*-methylformyl "cap" to each glucose substituent appears to change the relative orientation of some glucose fragments from that found in the X-ray structure of β-cyclodextrin.[8g] This we believe, in light of the work presented here and below, is a consequence of the cyclodextrin substructure falling into a lower symmetry, lower energy minimum rather than due to any special bonding features attributable to the *N*-methylformyl groups themselves. On a related note, Venanzi stated "...in fragments 1 and 4 the caps move out (away from the macrocycle) causing the secondary hydroxyls to move in toward the center of the cavity. In fragment 6, the secondary hydroxyls move out, while the caps move in...". Thus, Venanzi should be credited with first recognizing the in out isomerization of cyclodextrins described above. The implication of all this is that the system prefers to exist with many of the primary OH's canted outward and the secondary OH's inward. In the gas phase, then, guest molecules may actually enter α-cyclodextrin from the primary OH orifice rather than the secondary OH orifice. Upon entering the cavity the guest can induce a major structural change in the host that gives rise to observed inclusion complexes. The orientation and location of guests, based upon semiempirical SCF molecular orbital calculations of electrostatic fields around α-cyclodextrin suggest dipolar interactions between guest and host should be minimized[21] but these calculations do not indicate how the guest arrives. Our suggestion of

(21) See 7c and references cited therein.

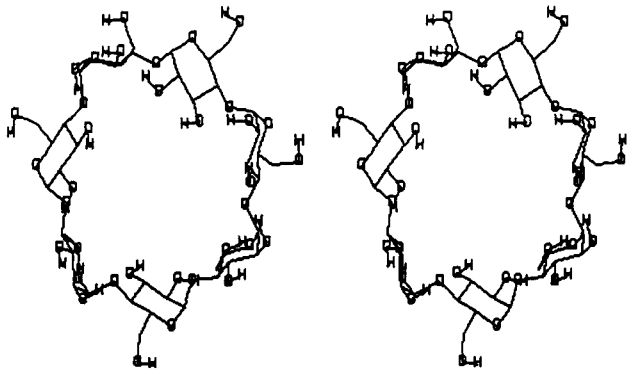

Figure 8. Stereographic view of "out" β-cyclodextrin **20**. The structure has C_1 symmetry and is viewed from the primary hydroxyl direction.

binding from the primary OH side has yet to be advocated but it is, based on the relatively small energy differences between the two inverted forms, plausible.

2. β-Cyclodextrin. Several asymmetric, low-energy structures for β-cyclodextrin could be found. Conformer **20** is the lowest energy structure available to β-cyclodextrin according to AMBER and is within 1 kcal mol^{-1} of the most stable structure according to MM2. Conformer **20** is presented in Figure 8, and its energy and torsion angles are listed in Table VII. This structure is similar to the one located by AMBER in our initial search for round, C_7 β-cyclodextrins (the 4.4 kcal mol^{-1} C_1 entry in Table I). Both MM2 and AMBER indicate the C_1 conformers of β-cyclodextrin to be substantially lower in energy than the highly symmetric C_7 form.

As in α-cyclodextrin, the view in Figure 8 highlights the fact that the primary OH side of the macromolecule's cavity is substantially opened. The ever-present hydrogen bonding network of secondary OH groups is also to be noted. Finally, we point out that in most of the out structures of α-, β-, and γ-cyclodextrins the pyran moieties tend to cant in and out in alternating fashion (see Figures 7–9). Since an odd number of units are involved in the β-cyclodextrin this alternating in–out structural feature can not be completely fulfilled. Still, where possible, it does exist.

3. γ-Cyclodextrin. Two low-energy conformations of γ-cyclodextrin were found. The first, **21**, has C_4 symmetry and the second, **22**, has C_2 symmetry. These structures are depicted in Figure 9 and their energies and torsion angles are listed in Table VII. MM2 indicates the C_2 structure to be the most stable conformation of all γ-cyclodextrin forms located. The C_4 structure, according to MM2, is within 1 kcal mol^{-1} of the global minimum. In contrast, AMBER indicates the C_4 out form to be the most stable conformation of γ-cyclodextrin. Indeed, the C_2 conformation routinely reverted to the C_4 conformation during several attempts to locate a C_2 structure by AMBER. The key point we make is, independent of force field, that symmetry breaking lowers the energy of the C_8 γ-cyclodextrin; i.e., the highly symmetric C_8 conformation is not its most stable shape.

As in the other cyclodextrins there exists an alternating canting of pyran units into and out of the macromolecular cavity, and, the homodromic ribbon of secondary OH hydrogen bonding is evident. Furthermore, the most open orifice is that associated with the primary OH side rather than the secondary OH side. Although MM2 implicates these out conformers to be marginally more stable than the in structures, AMBER suggests these inverted forms of cyclodextrin to be substantially more stable than the others. In any event, the C_8 symmetric shape of γ-cyclodextrin is far from the most stable conformation.

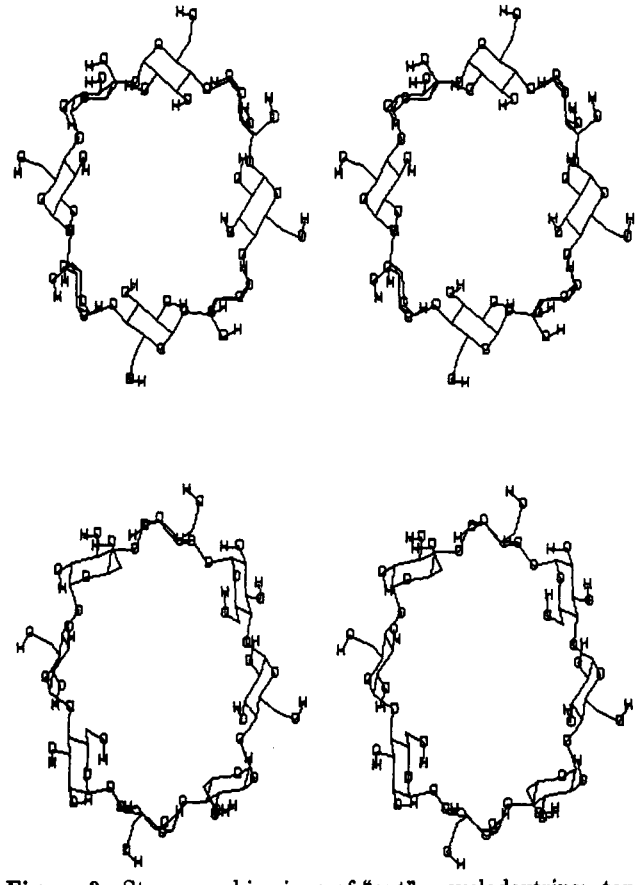

Figure 9. Stereographic views of "out" γ-cyclodextrins: top, γ-cyclodextrin **21** with C_4 symmetry; bottom, γ-cyclodextrin **22** with C_2 symmetry. Views are from the primary hydroxyl direction.

Summary

An analysis of the inherent conformational preferences of cyclodextrins, void of waters of hydration and crystal-lattice effects, has been undertaken with empirical force fields. Several important findings need to be highlighted. First we find that C_n symmetric structures, where n = number of glucose units, are not the most stable structures as portrayed in the literature. Symmetry breaking lowers the energy of these molecules. Second, we note that g^- and g^+ structures can exist, often within the same conformer (see, e.g., **20** and **22**). The g^- forms are usually more stable. Third, the idea that the belt of acetal oxygens linking the monomers together prefers to be planar is incorrect. In the lowest energy conformers located the puckering can be substantial. Fourth, and heretofore not yet fully discussed in the literature, is the finding that low-energy structures exist with the pyran groups canted away from the macromolecule's interior. This results in the secondary OH groups being tilted inward (presumably to enhance the network of secondary OH hydrogen bonding). Consequently a significant opening of the primary OH rim of the cyclodextrin cavity is found. Binding of guests under nonequilibrium conditions (as in gas chromatography) may find association with the primary hydroxyls more amenable than the secondary hydroxyls. Some of the peculiar reversals in retention order noted by Armstrong may be rationalized this way.[10j] Finally, the cyclodextrins, as a unique class of macromolecules, can adopt a wide range of shapes, most of which will be populated under gas chromatographic conditions. Although we did not consider the activation barriers separating these minima explicitly,

many of the transits from high-energy conformations to low-energy ones appear to have relatively low barriers. Overall, then, we find these compounds to be remarkably flexible rather than rigid. The highly symmetric cyclodextrin structures portrayed in the literature are to be regarded as time-averaged structures only.

The conclusions derived from this study and the relationship to the recognition process of cyclodextrins depends on the quality of the force field used. The AMBER and MM2 force fields seem to treat hydrogen bonding in alcohols along with the anomeric effect quite well. Furthermore, both AMBER and MM2 are in qualitative agreement so the results of our study are force field independent. The question of water and its influence on cyclodextrin structure as well as its influence on inclusion complexation has not been addressed here. It is not known whether the GC phases used in chromatography are partially hydrated or completely unhydrated as we assume here. Also, with regard to the recognition process of cyclodextrins, one should consider a Boltzman distribution of the conformational states described here along with the symmetry of the included guest. To address these issues we are performing molecular dynamics simulations to derive averaged structures and energies of guest–host complexes.[22] The results of in vacuo simulations along with partially hydrated and fully solvated conditions are being examined with the CHARMM force field to understand the role of water on complexation of enantiomeric guests.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-8901828) and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No. α-CD, 10016-20-3; β-CD, 7585-39-9; γ-CD, 17465-86-0.

Supplementary Material Available: Component energies for structures 1–3 in Table I and structures listed in Tables II–VII (7 pages). Ordering information is given on any current masthead page.

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Theoretical Studies of Radical Recombination Reactions. 4. An AM1/CI Study of Reactions of Benzylic and Allylic Radicals. An Intrinsic Barrier to Bond Formation

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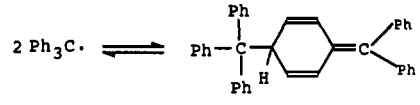
Received May 28, 1991

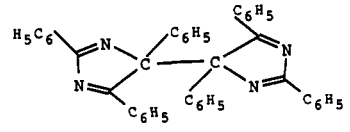
AM1/CI calculations on the reaction paths for the coupling of organic free radicals are presented. The calculations are in good agreement with previously reported experimental results for benzyl radical coupling. Selectivities for the combinations of methyl radicals with allyl, azaallyl, benzyl, and variously cyano-substituted benzyl radicals as well as seven different coupling reactions of two benzyl radicals are reported. Application of Marcus theory and a fitting to a linear equation after Leffler and Grunwald suggest the existence of an intrinsic barrier of 22 or 25 kcal/mol, respectively, for the coupling of carbon-centered free radicals.

The recombination of two free radicals to form a single covalent bond is often thought to occur without activation. This conception is probably due to analogy with the combination of two atoms, such as H, to form a covalent molecule, such as H_2. Exceptions to this idea are usually attributed to steric interactions alone. Nevertheless, experimental observations that have long been in the literature suggest that other effects, presumably electronic in nature, might also contribute to barriers to combination of radicals. In fact, the first free radical characterized, triphenylmethyl, has long been known to be in equilibrium with its dimer, which has been shown to have structure I, rather than the originally anticipated hexaphenylethane.[1]

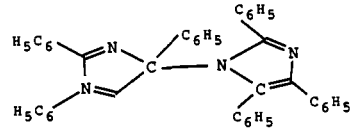


I

Also prominent among the experimental observations that support this idea are the observed selectivities for attacks at radicals that can, in principle, react at more than one site. Thus, allyl radical reacts at the terminal positions, rather than the central carbon (to give cyclopropyl products), and benzyl radicals couple predominantly at the α-carbons, rather than at the ring carbons. A particularly striking example involves the coupling of triphenylimidizoyl radicals, which combine to form two different products, one kinetically and the other thermodynamically favored.[2] The kinetically favored product, II, is clearly more sterically hindered than the thermodynamic product, III.



II



III

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