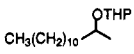
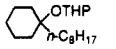
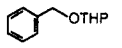
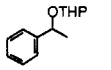
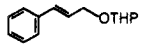
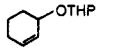
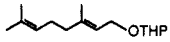
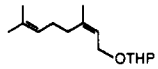
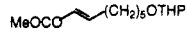
Table I. Thiostannane-Promoted Deprotection of THP Ethers

entry	1	2 (equiv)	reaction temp, °C	reaction time, h	alcohol yield,[a] %
1	n-$C_{12}H_{25}$OTHP	**2a** (1.1)	-20	3	(97)
2	n-$C_{12}H_{25}$OTHP	**2b** (0.55)	-20	1.5	97 (100)
3	n-$C_{12}H_{25}$OTHP	**2c** (0.6)	0	16	(100)
4		**2c** (0.6)	0	16	84 (100)
5		**2c** (0.6)	0	9	80 (86)
6		**2c** (0.8)	0	16	(70)
7		**2c** (0.8)	0	16	(82)
8		**2c** (0.8)	0	16	90
9		**2c** (0.6)	0	18	(81)
10		**2c** (0.8)	-20 to 0	12	70 (85)
11		**2c** (0.8)	-20 to 0	12	(82)
12	^{t}BuMe$_2$SiO-$(CH_2)_6$OTHF	**2c** (0.8)	0	16	88
13	AcO$(CH_2)_6$OTHP	**2c** (0.8)	0	16	97
14	CH_3SO_3-$(CH_2)_6$OTHP	**2c** (0.8)	0	16	90
15	MOMO-$(CH_2)_6$OTHP	**2c** (0.8)	0	25	89
16		**2c** (0.8)	0	11	80

[a] Isolated yields. GLC yields are given in parentheses.

this temperature. GLC analysis of the solution indicated formation of 1-dodecanol in 100% yield. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated. Column chromatography of the residue on silica gel (hexane–ethyl acetate, 97:3 to 70:30) afforded 1-docecanol (180 mg, 97%) and 2-(phenylthio)-tetrahydropyran (190 mg, 98%).[17]

Deprotection of EE Octyl Ether. To a toluene solution (4 mL) of EE octyl ether (203 mg, 1 mmol) and **2b** (204 mg, 0.56 mmol) was added **3** (1.0 M toluene solution, 1 mL, 1 mmol) at 0 °C. The mixture was stirred for 9 h at this temperature. Aqueous workup provided octanol in 87% based on GLC.

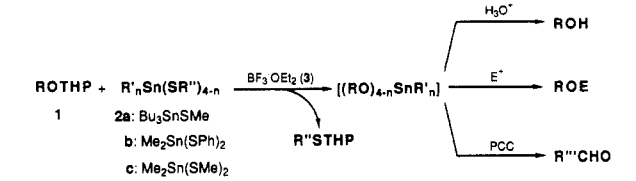
Attempted Deprotection of 2-Phenyl-2-(tetrahydropyran-2-yloxy)propane. To a toluene solution (3 mL) of 2-phenyl-2-(tetrahydropyran-2-yloxy)propane (220 mg, 1 mmol) and **2c** (136 mg, 0.56 mmol) was added **3** (1.0 M toluene solution, 1 mL, 1 mmol) at 0 °C. The mixture was stirred for 4 h at this temperature and poured into aqueous $NaHCO_3$. The mixture was extracted with benzene. Drying (Na_2SO_4), evaporation, and column chromatography (hexane) afforded 2-(methylthio)-2-phenylpropane (141 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 6 H), 1.76 (s, 3 H), 7.20–7.60 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.3, 29.4, 46.6, 126.3, 126.4, 128.0, 146.1; HRMS calcd for $C_{10}H_{14}S$ 166.0816, found 166.0771.

1-Methyl-1-(tetrahydropyran-2-yloxy)-2-cyclohexene was subjected to the same reaction to give 1-methyl-3-(methylthio)-1-cyclohexene in 99% yield: ^{1}H NMR ($CDCl_3$) δ 1.55–1.75 (m, 2 H), 1.65 (s, 3 H), 1.80–1.95 (m, 4 H), 2.08 (s, 3 H), 3.28 (m, 1 H), 5.44 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.1, 23.8, 28.2, 29.8, 42.5, 121.8, 137.4; HRMS calcd for $C_8H_{14}S$ 142.0816, found 142.0840.

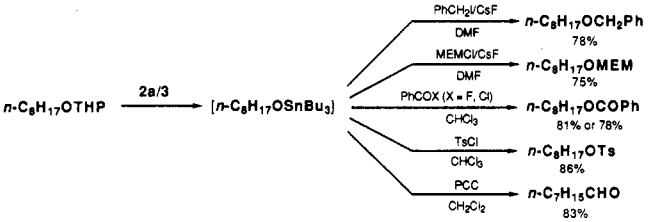
Subjection of *trans*-1-phenyl-3-(tetrahydropyran-2-yloxy)-1-butene to the same reaction afforded, after 3 h, 98% yield of *trans*-3-(methylthio)-1-phenyl-1-butene: ^{1}H NMR ($CDCl_3$) δ 1.41 (d, 3 H, J = 6.6 Hz), 2.01 (s, 3 H), 3.37 (m, 1 H), 6.04 (dd, 1 H, J = 8.8 and 15.7 Hz), 6.34 (d, 1 H, J = 15.7 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 20.1, 43.9, 126.1, 127.3, 128.4, 129.4, 131.7, 136.6; HRMS calcd for $C_{11}H_{14}S$ 178.0816, found 178.0796.

Conversion to Benzyl Ether. To a toluene solution (4 mL) of octyl THP ether (215 mg, 1 mmol) were added **2a** (371 mg, 1.1 mmol) and **3** (1.0 M toluene solution, 1 mL, 1 mmol) at 0 °C, and

Scheme I



Scheme II



the solution was stirred for 7 h. The solvent was evaporated in vacuo, and then DMF (5 mL) was added. To this solution were added benzyl iodide (297 mg, 1.3 mmol), CsF (198 mg, 1.3 mmol), and MS 3A (200 mg). The reaction mixture was stirred for 20 h at room temperature and poured into water. The mixture was extracted with ethyl acetate. After drying (Na_2SO_4) and evaporation, GLC analysis of the residue indicated formation of benzyl octyl ether in 78% yield.

Conversion to MEM Ether. To a DMF solution obtained according to the completely same procedure as above were added MEM chloride (436 mg, 3.5 mmol), CsF (228 mg, 1.5 mmol), and MS 3A (200 mg). The reaction mixture was stirred at room temperature for 12 h. The workup as described above afforded 75% yield of MEM octyl ether based on GLC analysis.

Conversion to Benzoate. The reaction of **1**, **2**, and **3** was carried out in the same way as above. Then, the toluene solvent was replaced by chloroform (5 mL). To this solution were added benzoyl fluoride (310 mg, 2.5 mmol) and MS 3A (200 mg). The mixture was stirred for 70 h. The workup analogous to the above operation afforded octyl benzoate (81% based on GLC). When benzoyl chloride was employed, the yield was 78%.

Conversion to Tosylate. The manipulation was analogous to the benzoylation except that tosyl chloride (381 mg, 2 mmol) was employed in place of benzoyl fluoride and that the reaction temperature was maintained at 40 °C for 70 h. The yield of the tosylate was 86% based on GLC. Column chromatography (hexane–benzene, 95:5) afforded the isolated product (218 mg, 77%).

Conversion to Aldehyde. The initial toluene solvent was replaced by dichloromethane (5 mL). To this solution was added PCC (432 mg, 2 mmol) and MS 3A (200 mg). The reaction mixture was stirred at room temperature for 10 h. The usual workup afforded octanal (106 mg, 83%).

Acknowledgment. This work was partially supported by Grant-in-Aid from The Ministry of Education, Science, and Culture, Japan. We are also grateful to T. Tada for his technical assistance.

Solution Geometry of β-Cyclodextrin–1-Bromoadamantane Host–Guest Complex As Determined by ^{1}H{^{1}H} Intermolecular NOE and MM2 Calculations

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Host–guest chemistry[1-4] is gaining widespread interest because of its obvious implications in molecular recogni-

0022-3263/90/1955-4772$02.50/0

Table I. Experimental NOE Values

	% NOE[a,b]								
H_{irr}	H-α	H-β	H-γ	H-1	H-2	H-3	H-4	H-5	H-6a,6b
H-α		0.0	6.1	0.0	0.0	2.3[c]	0.0	0.7	?
H-β	0.0		7.5	0.0	0.0	?[d]	0.0	0.8	?[d]
H-γ	2.0	2.2		0.0	0.0	?[d]	0.0	0.4	?[d]
H-1	0.0	0.0	0.0		4.3	0.0	6.1	0.3	0.2
H-5	1.0	2.6[e]	2.1	0.5	0.0	?[d]	0.0		?[d]

[a] For numbering, see Figure 2. [b] Solvent, 100% D_2O; T, 42 °C. [c] Including a small amount of NOE on H-6a,6b. [d] Reliable assignment of % NOE was not possible because confusing overlap of signals due to H-3 and H-6a,6b. Thus, selective presaturation of H-3 was not achieved. [e] Only β equatorial protons of **2** were considered.

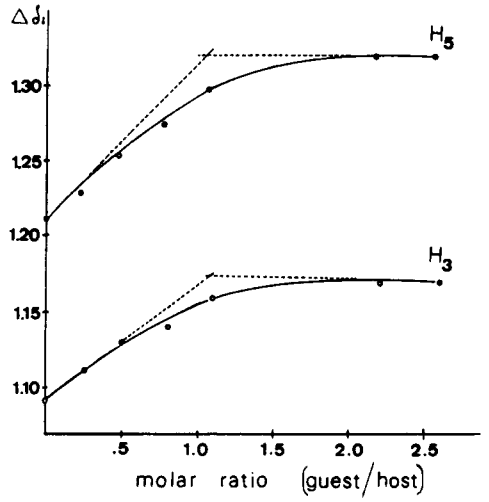

Figure 1. Graph of the chemical shifts (error range ±0.02 ppm) of the β-cyclodextrin inner protons as a function of guest to host molar ratio, in aqueous solution. $\Delta\delta_i = \delta(\text{H-1}) - \delta_i$.

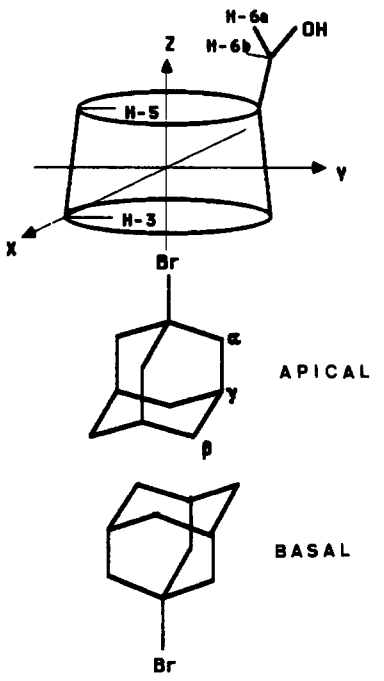

Figure 2. Schematic representation of β-cyclodextrin and 1-bromoadamantane showing the orientation used in this work as well as the different approximations (basal and apical). Nomenclature of protons is also shown.

tion, substrate–receptor interactions, binding, and, in general, supramolecular chemistry.[5] In addition, cyclodextrin (CD) inclusion compounds have been widely studied,[6-8] and their use has been proposed as a method to overcome the low bioavailability of insoluble or unstable pharmaceuticals.[9,10] A number of cyclodextrin complexes, mainly with aromatic derivatives, have been studied in recent years by an array of physical and chemical methods, including X-ray[11] or neutron diffraction.[12] On the other hand, several approaches to establish the geometries of host–guest complexes in solution have been published (^1H and ^{13}C chemical shifts[13,14] and relaxation times dependences,[15,16] $^1H\{^1H\}$ NOE experiments,[17] kinetic and thermodynamic[18-21] measurements, and, more recently, CNDO[22,23] and molecular mechanics (MM)[24,25] calculations).

Molecular geometries can be determined either theoretically (i.e., by MM calculations) or experimentally (i.e., NOE values[26,27] give the relative inter- or intramolecular distances). The agreement between theoretical results and experimental data can be a powerful way to determine the geometry of a complex in solution. We now report the formation of the 1:1 complex (**1**) of 1-bromoadamantane

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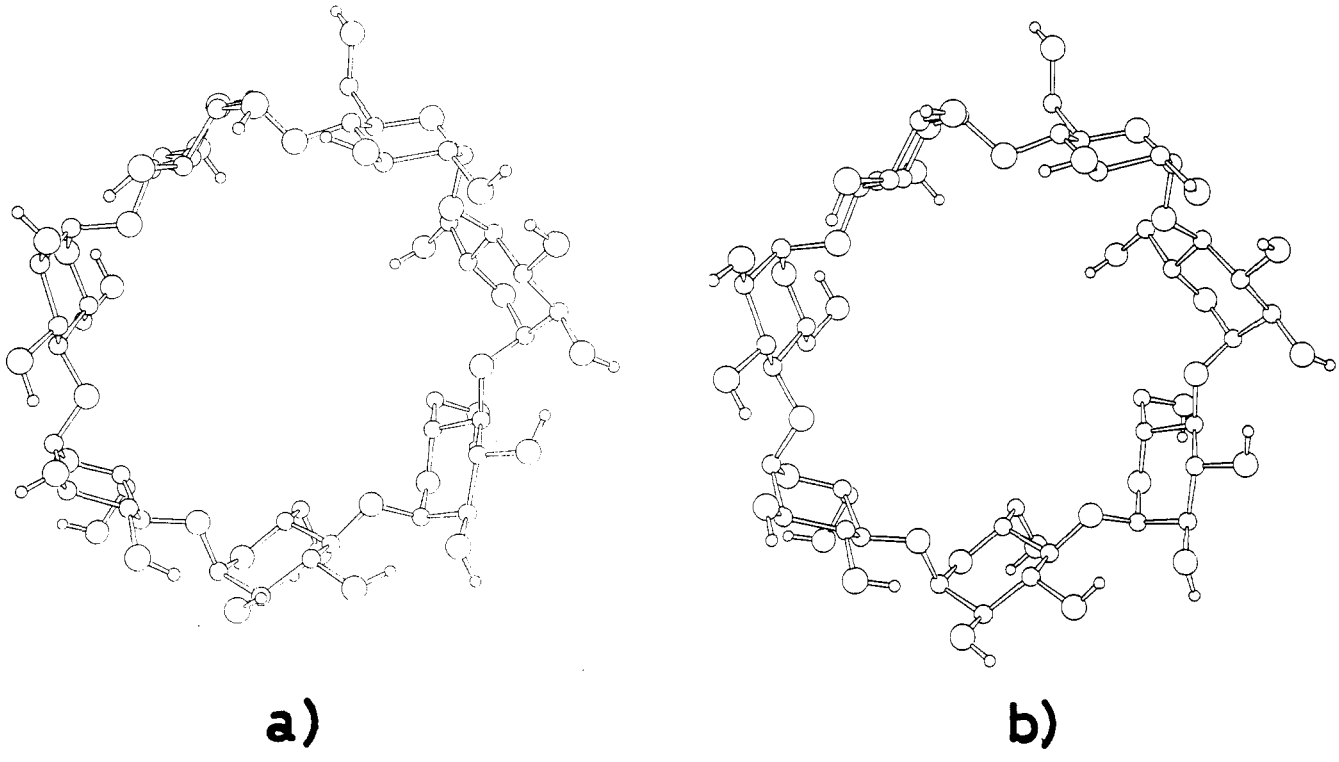

Figure 3. ORTEP[35] representation of the β-CD structure: (a) experimental structure determined by neutron diffraction (water molecules have been excluded for clarity); (b) MM2 fully optimized structure.

(2) with β-cyclodextrin (3) in aqueous solution as well as the results of MM2 calculations and NMR determinations (chemical shifts and inter-/intramolecular NOEs) of 1.

NMR Determinations

Figure 1 shows the chemical shifts of the macrocycle inner protons (H-3 and H-5) as a function of guest to host molar ratio. A continuous shielding of these protons until 1:1 ratio was achieved was observed. No changes were detected for the chemical shifts of the outer β-cyclodextrin protons, and the coupling constant $J_{1,2}$ was also found invariable at 3.7 Hz. The dissociation constant for the 1:1 complex (1) was estimated by simulation from the $\Delta\delta/R$ data (R = guest to host molar ratio), using the method of Wood et al.[13] and Inoue et al.,[14] and was found to be approximately 10^{-3} mol L^{-1}.

Intermolecular NOEs having values larger than 0.2% are exclusively found for H-α,β,γ/H-3,5 pairs (and the overlapping H-6a,b protons, which absorb partly at the H-3 frequency) (Table I), thus confirming that the guest is inside the host cavity. Furthermore, irradiation of H-α produced a much larger NOE at H-3 (2.3%) than at H-5 (0.7%), thus suggesting the basal approach (see below) shown in Figure 2. This is also consistent with the NOEs found for H-6a,6b upon selective presaturation of H-β and H-γ. However, the simultaneous (nonquantifiable due to overlapping with the H-6a,6b absorption) NOE at H-3 can be justified by invoking some contribution from the apical arrangement (see Figure 2). This result is not surprising given that enzyme models with catalysts anchored on both the primary and secondary sides of 3 do give reaction rate accelerations.[28,29] Finally, the intramolecular NOE at H-4 upon irradiation of H-1 is of interresidue origin, since its value (6.1%) is larger than the simultaneous NOE on H-2 (4.3%).

Theoretical Calculations

Calculations on Isolated β-CD. β-CD structure has been studied by several experimental methods,[13-15,17,18b,22,30,31] but always complexing some other molecule(s) (like water).[20] The experimental determination of the undecahydrate complex was made by neutron diffraction[12] and shows the presence of two water molecules in the β-CD cavity making H bonds with some of the hydroxyl groups.

The coordinates of this experimentally determined β-CD were taken as the starting point for our MM2 calculations. After the published values were refined,[32] the experimentally undetermined hydrogen atoms and all the lone pairs of electrons needed for MM2 calculations were added. The neutron diffraction structure denotes the presence of intramolecular hydrogen bonds between the C_2-OH of one glucose and the C_3-OH of the adjacent glucose unit. However, the MM2(77) force field does not consider hydrogen bonding, and consequently this should be explicitely included to obtain reasonable agreement between the experimental and MM2 calculated geometry of the β-CD torus.

From the different possible approaches of treating H bonding under the MM scheme (electrostatic interactions, dipole–dipole interactions, van der Waals interactions, and specific bonds between H type 21 and O type 6 or LP type 20), we chose the last one because we were not interested in reproducing the stabilization coming from H-bond formation but only in fixing the β-CD geometry. After searching for the suitable lone pairs to form the H bonds, we defined a completely new atom type (type 49) as well as the hydroxylic hydrogens involved in the H bonds (type

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(32) The *Y* coordinate for HO-64 should be of positive value while the *Z* coordinate for O-46 should be negative in ref 12.

Table II. Calculated[34] and Experimental Averaged Distance Ratios from H-5 to Pairs of Guest Protons

dist,[b] Å	r_i/r_j[a] H-β_t/H-γ	H-β_{eq}/H-γ	H-β_t/H-α	H-β_{eq}/H-α	H-γ/H-α	rms
			Basal			
−3	1.020	1.041	0.694	0.709	0.681	0.063
−2	1.077	1.044	0.750	0.727	0.696	0.053
−1	1.118	1.013	0.818	0.742	0.732	0.040
0	1.072	0.967	1.055	0.952	0.984	0.030
+1	1.081	0.980	1.270	1.151	1.175	0.089
+2	1.062	0.975	1.582	1.453	1.490	0.179
+3	1.049	0.972	1.606	1.487	1.531	0.189
			Apical			
−3	1.037	0.974	1.432	1.345	1.381	0.144
−2	1.040	0.971	1.507	1.406	1.449	0.164
−1	1.045	0.967	1.610	1.490	1.540	0.191
0	1.039	0.952	1.652	1.514	1.590	0.202
+1	1.020	0.925	1.460	1.323	1.431	0.150
+2	1.037	0.934	1.106	0.997	1.067	0.048
+3	1.079	0.991	0.922	0.846	0.854	0.009
+4	1.503	0.989	0.706	0.663	0.670	0.064
exptl[c]	1.080	0.962	0.954	0.850	0.883	–

[a] H-β_t means that both β protons (axial and equatorial) are included in the calculation of r_i/r_j, and H-β_{eq} means that only β equatorial protons are considered. [b] From MM2 calculations. [c] From NOE values upon irradiation of H-5.

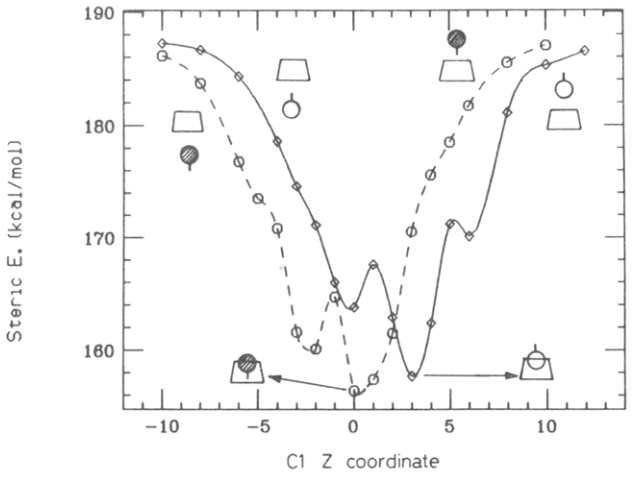

Figure 4. Plot of the total steric energy vs the distance of C-1 to the XY plane (see Figure 2). 1-Bromoadamantane is represented by open (or shaded) circles and β-cyclodextrin by the open rhombus representation. Key: solid line, apical approximation; dashed line, basal approximation.

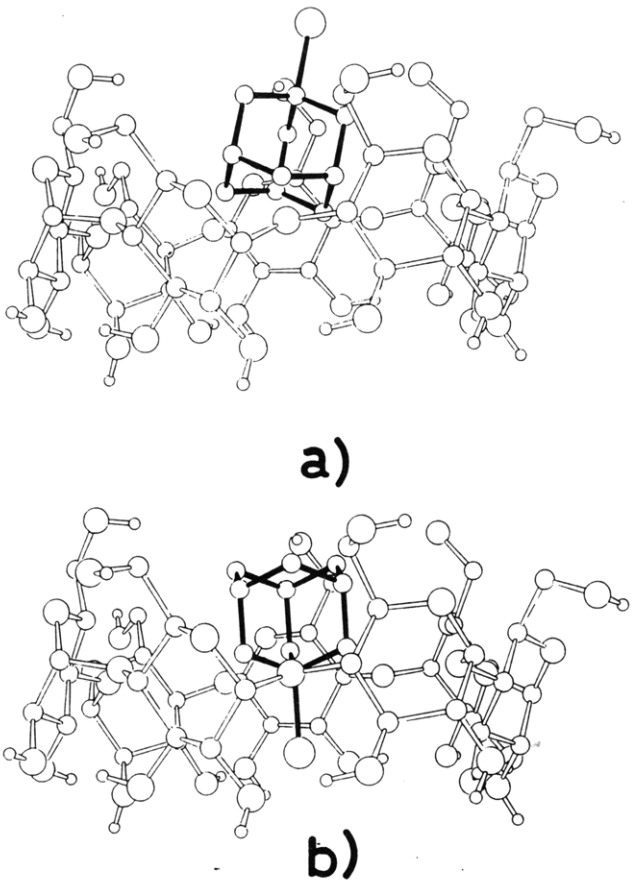

Figure 5. ORTEP[35] representation of the calculated global energy minima of 1. Hydrogens other than hydroxylic ones have been removed for clarity. Key: (a) apical approximation; (b) basal approximation.

48). Parameters used in these calculations were taken from the work of Oki et al.[33]

The MM2-optimized structure of β-CD perfectly agrees with the experimental one (Figure 3). Only small changes are observed on the primary hydroxyl groups as a clear consequence of considering neither intra- nor intermolecular H bonds with the molecules of water present in the experimental structure. The calculated β-CD shape is a truncated cone, with all seven glycosidic oxygens almost in a plane, forming a quasi regular heptagon that can be inscribed into a circle of 5.00-Å radius. The H-3 protons define the widest entrance (4.38-Å radius) and H-5 protons are at the narrowest part of the molecule (4.07-Å radius). Please note that these radii are distances from the β-CD 7-fold axis of symmetry (Z axis).

Calculations on the Complex. The β-CD molecule was oriented so as to have almost all glycosidic oxygens in the XY plane and the CH_2OH groups on the positive (upper) region of the Z axis (Figure 2). The inclusion of **2** was simulated by moving one molecule of the guest along the Z axis. Each calculated point was fully optimized except for the C-1 in adamantane, which was kept on the Z axis (from −10 to +12 Å) at the predetermined distance to the XY plane (seven glycosidic oxygens). Two possible orientations for **2** were considered: (a) apical and (b) basal, depending on whether the bromine atom enters into the secondary side of the β-cyclodextrin cavity the first or the last (Figure 2).

Figure 4 contains the representation of total steric energy vs the Z coordinate of C-1 for both approximations

(33) Abe, K.; Hirota, M.; Yamamoto, G.; Oki, M. *Chem. Lett.* **1984**, 665.

of 1-bromoadamantane. Apparently, the binding is exothermic by ca. 30 kcal/mol. One reason for this large value may be the absence of solvent in the calculations (solvent molecules would greatly stabilize the separated host and guest). The global energy minima are at C-1 Z coordinates of +3 Å for the apical and at 0 Å for the basal approaches (Figure 5). In both cases the guest is in the narrower half of the host cavity. The two relative energy maxima at C-1 Z coordinates of +1 and +5 Å for the apical approach are due to interactions of adamantane hydrogens with the inner protons of β-CD (H-α/H-5 and H-β_{eq}/H-6 in +1 Å and H-β_{eq} + H-γ/H-6 in +5 Å). Similarly, the relative maximum at C-1 Z coordinate of −1 Å for the basal approach is produced by facing H-β_{eq} with H-5. According to energetic and steric considerations, compound **2** should enter into the cavity of **3** in the basal orientation through the wide (secondary hydroxyl) entrance because both global minima are separated by 1.4 kcal/mol. Of course, the same final result could also be reached by means of an apical approach through the narrow (primary hydroxyl) entrance.

Discussion

The host–guest complex can be described by several internuclear mean distances from an equilibrium pattern. The free rotation of the guest about the Z axis inside the host hollow was determined by MM2 calculations and resulted in a maximum barrier of ca. 2 kcal/mol. This value justifies the average of the complex signals on the NMR time scale. A set of calculated distance ratios was derived with use of Bendall et al.'s approach[34] with the interproton distances obtained in the MM2 calculations. Table II contains these ratios for several positions near both calculated minima of **1**; the rms deviations with experimental ratios (derived from NOE values after selective irradiation of H-5) are also given. It is remarkable that the smallest rms deviation corresponds to the MM2-calculated minimum for each approximation.

Conclusions

The toroidal shape of crystalline β-CD has been correctly reproduced by the MM2 calculations with artificial hydrogen bonds between selected secondary hydroxyls. There are no significant hydrogen bonds and no important electrostatic forces between host and guest in this complex as deduced from careful inspection of molecular models. No energetic considerations on complex formation can be done due to the absence of solvent in the calculations. However, the results obtained in this work are at least qualitatively useful. Moreover, the hydrophobic nature of our guest suggests that solvation effects will aid in the formation of the complex but will probably not intervene in the final structure. The results of our work (MM2 calculations and NOE experiments) show that **2** does not enter into **3** in only one way. Rather, they predict that **2** is situated mainly in the narrower half of the torus cavity, with the bromine atom pointing toward the widest entrance and the apical carbon atom C-1 located on the equatorial plane of the macrocycle. Combination of MM2(77)-calculated geometries with NOE determinations is, thus, a useful tool for the topological study of these cyclodextrin host–guest complexes.

Experimental Section

The samples were prepared by mixing weighted amount of **2** and **3** (twice lyophilized in D_2O to deuterate all the OH protons). In order to ensure the dissolution of **2**, samples had to be heated in a good ultrasonic bath, at ca. 45 °C. All spectra were obtained on a Bruker AM400WB spectrometer, in a 5-mm dual-probe thermostated at 42 °C, with 100% D_2O as solvent; the complex concentration was 0.014 M.

^{1}H NMR (D_2O, TMS external standard, 400 MHz): (**1**) δ 4.99 (d, J = 3.7 Hz, 7 H, H-1), 3.57 (dd, J = 9.4 Hz, J' = 3.7 Hz, 7 H, H-2), 3.80 (dd, J = 9.4 Hz, J' = 9.4 Hz, 7 H, H-3), 3.50 (dd, J = 9.4 Hz, J' = 9.2 Hz, 7 H, H-4), 3.69 (dq, J = 9.2 Hz, J'' = 4.0 Hz, J'' = 2.0 Hz, 7 H, H-5), 3.79 (dd, J = 12.8 Hz, J' = 4.0 Hz, 7 H, H-6a), 3.83 (dd, J = 12.8 Hz, J' = 2.0 Hz, 7 H, H-6b), 2.22 (br, 3 H, H-γ), 1.74 (br, 6 H, H-α), 1.64 (br, 6 H, H-β); (**2**) δ 2.04 (br, 3 H, H-γ), 1.64 (br, 6 H, H-α), 1.57 (d, J = 13.0 Hz, 3 H, H-β_{eq}), 1.51 (d, J = 13.0 Hz, 3 H, H-β_{ax}); (**3**) δ 4.99 (d, J = 3.7 Hz, 7 H, H-1), 3.57 (dd, J = 9.4 Hz, J' = 3.7 Hz, 7 H, H-2), 3.88 (dd, J = 9.4 Hz, J' = 9.4 Hz, 7 H, H-3), 3.50 (dd, J = 9.4 Hz, J' = 9.2 Hz, 7 H, H-4), 3.79 (br, 7 H, H-5), ca. 3.83 (br, 14 H, H-6a + H-6b).

NOE difference spectra were obtained with overnight accumulation (about 1400 scans/FID), with a presaturation time of 7–10 s. The selective presaturation of H-5 was performed with fast alternating irradiation over each resonance site of the multiplet.

Computational Details. Calculations were performed with a MM2PRIME[36] program executed on a VAX 8800 computer. Allinger's MM2(77)[37] force field together with MM2(85) parameters have been used throughout this work. Parameters for the hydrogen bond simulation were taken from ref 33. Calculations were done in vacuo, and structures were minimized with use of the default optimization criteria. About 2.5 h of cpu time was required to achieve a minimized structure for the isolated host. The host–guest supermolecule needed about 5 min cpu time for every point except for those with C-1 Z coordinates between +3 and −3 Å, which needed about 1.5 h. Two limitations must be considered: (a) Calculations were performed for systems in the gas phase; solvation effects were simply not considered. (b) β-CD has a total of 28 bonds capable to rotate (21 hydroxyls and 7 C-COH in primary hydroxyls); fortunately, we are using real bonds to simulate hydrogen bonds, and the number of rotating bonds is reduced to 14. We mitigated the problem by consistently initiating the calculations with the identical "minimized" β-CD structure (coming from the optimization of the isolated host).

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