Stereodynamics of 4,6,10,12,16,18,22,24-Octamethylcalix[4]arene

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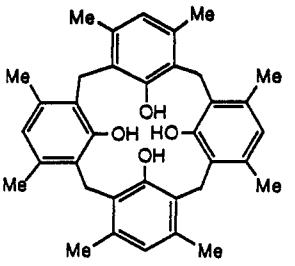
The dynamic stereochemistry of 4,6,10,12,16,18,22,24-octamethyl-25,26,27,28-tetrahydroxycalix[4]arene (**2**) is analyzed. The measured barrier for the coalescence of the diastereotropic methylene protons (10.9 kcal mol^{-1}) and the coalescence of the methyl signals (10.7 kcal mol^{-1}) is identical. It is concluded that the dynamic pathway observed by NMR corresponds to a ring-inversion process which exchanges both the methylene protons and the symmetry nonequivalent "perpendicular" and "coplanar" aryl rings. Molecular mechanics calculations satisfactorily reproduce the boat conformation of **2** and indicate that the presumed transition state for the pseudorotation process lies 27 kcal mol^{-1} above the ground state. In contrast to the parent *p-tert*-butylcalix[4]arene (**1**), changing the solvent from $CDCl_3$ to pyridine-d_5 raises the inversion barrier of **2**. Calixarene **2** crystallizes from pyridine as a 1:1 complex in which the calixarene molecule exists in a boat conformation and the pyridine molecule is partially included in the calix cavity. Fixation of the conformation of **2** was obtained by preparing the 1,3-dimethyl ether derivative **6** by alkylation of **2** under phase-transfer catalysis conditions. The conformation of **6** in the crystal is similar to that of **2**, with the two methoxy groups located in the "perpendicular" rings. The inversion barrier of **6** is higher than 24.0 kcal mol^{-1} as estimated by saturation transfer experiments.

Introduction

During the last years there has been an intense interest in synthetic organic host molecules.[1] Calix[*n*]arenes,[2] cyclic oligomers made of *n* phenol and methylene units, occupy a privileged position in this family since by choosing carefully the reaction conditions they can be prepared in a single step by condensation of substituted phenols and formaldehyde under basic catalysis.[3]

The conformational behavior of calix[4]arenes is commonly analyzed in terms of four ideal conformations: "cone", "partial cone", "1,2-" and "1,3-alternate".[2] Spectroscopic as well as crystallographic evidence indicates that the preferred conformation of the parent compound *p-tert*-butyl-calix[4]arene (**1**) is the "cone".[4]

We have recently reported in a preliminary communication the preparation and structure of the sterically crowded 4,6,10,12,16,18,22,24-octamethyl-25,26,27,28-tetrahydroxycalix[4]arene (**2**) abbreviated as octamethylcalix[4]arene.[5] Calixarene **2** was prepared by reaction of either 2,6-dimethyl-4-hydroxybenzyl alcohol or 2,4-dimethyl-6-hydroxybenzyl alcohol with $AlCl_3$ in nitrobenzene at 90 °C.[6] X-ray diffraction of the DMF solvate of **2** showed that in contrast to the parent compound **1**, **2** exists in the crystal in a "boat" conformation in which two opposite rings are nearly coplanar with the main macrocyclic plane ("coplanar" rings) whereas the remaining two rings are nearly perpendicular to this plane ("perpendicular" rings). In this paper, we report the solution conformation and dynamic stereochemistry of **2**, its solid-state inclusion behavior, and the preparation and crystal structure of its dimethyl ether derivative.



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Results and Discussion

Static Stereochemistry of 2. Although the crystallographic data indicate that **2** exists in the solid state in a boat conformation, the solution conformation could be different. It was therefore of interest to determine the NMR spectrum under conditions in which any conformational process is frozen. Since the presence of a boat conformation should affect the hydrogen bonding pattern, we determined also the IR spectrum of **2**.

(a) NMR Spectra. The ^1H NMR spectrum of a sample of **2** in $CDCl_3$ at room temperature displays single signals for the aromatic (δ = 6.51), methylene (δ = 3.80), methyl (δ = 2.25), and OH (δ = 8.19) protons. The ^{13}C NMR spectrum displays four signals for the aromatic carbons (δ = 122.6, 125.3, 135.4, 152.5) and one signal each for the methyl and methylene carbons (δ = 24.5, 20.0). The NMR spectra are in agreement with a species that is conformationally mobile on the NMR time scale at room temperature, in contrast to **1** which exists at room temperature as a slowly inverting cone on the NMR time scale.[2] The increased flexibility of **2** compared to **1** can be ascribed to the increased groud-state energy of **2** due to the steric repulsions between the methyl groups at neighboring rings as well as to the presence of weaker intramolecular hydrogen bonds (see below) which hold the conformation. To see whether the dynamic process can be frozen, a sample of **2** in $CD_2Cl_2/CDCl_3$ (1:1) was cooled to 192 K. Calixarene **2** displays in the ^1H 200-MHz NMR spectrum two signals each for the OH groups (δ = 8.62, 9.06), aromatic protons (δ = 6.52, 6.56), and the methyl groups (δ = 2.04, 2.40), and two closely spaced doublets for the methylenic protons in agreement with a frozen "boat" conformation in solution of C_{2v} symmetry. The relatively upfield position

(1) For recent reviews on host guest chemistry, see: (a) Toner, J. L. In *Updates from the Chemistry of Functional Groups: Crown Ethers and Analogs*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1989. (b) Molecular Inclusion and Molecular Recognition–Clathrates I. Weber, E., Ed. *Top Curr. Chem.* **1987**, *140*. (c) *Synthesis of Macrocycles: Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987.

(2) For comprehensive reviews on calixarenes, see: Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. Gutsche, C. D. ref 1c, p 93. Gutsche, C. D. *Top. Curr. Chem.* **1984**, *123*, 1.

(3) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.

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(6) The amount of $AlCl_3$ to be added for the synthesis of **2** should be 0.277 g and not 0.277 mg as stated in in ref 5. The calculated yield should be 34% and not 28% as stated.

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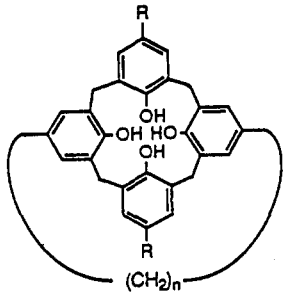
of the OH groups (δ = 8.19 ppm) as compared with **1** (δ = 10.2 ppm) can be ascribed to the weakening of the hydrogen bond between the OH groups as a result of the presence of the boat conformation in **2**.[7] It is interesting to note that whereas there is a large chemical shift difference for the diastereotopic methylene protons of calix[4]arene ($\Delta\delta$ = 0.71 ppm),[8] the $\Delta\delta$ value for **2** is relatively small and therefore under slow exchange conditions these protons appear as a somewhat unresolved AB quartet at 200 MHz.

(b) IR Spectrum. The IR spectrum of calix[4]arenes is characterized by a low stretching OH frequency (3150 cm^{-1}) due to the presence of a circular hydrogen bond.[2] A marked deviation of the calixarene from the cone conformation into a boat form should result in weakening of the hydrogen bond and a shift of the stretching frequency into larger wave numbers. Indeed, Böhmer and co-workers[9] have shown that the OH stretching frequency of calix[4]arenes bridged at two para positions at nonvicinal rings **3** shifts to higher frequencies with the decrease in length of the bridge and the progressive distortion of the cone conformation. For example, for systems **3** (n = 5–9) the OH stretching frequencies are ν_{OH}(KBr) = 3410, 3340, 3250, 3250, and 3210 cm^{-1}, respectively. For calixarene **2** ν_{OH} (KBr) is 3290 cm^{-1} and is analogous to the frequencies found for system **3** when n = 6 or 7.



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(c) Molecular Mechanics Calculations. Molecular mechanics calculations of calixarene **2** were performed using the MM2(85) program.[10] According to the calculations, the boat and 1,3-alternate conformations are of similar steric energies and are the lowest energy conformations. The 1,2-alternate and symmetric cone conformations have much higher steric energies and lie 5.3 and 31.2 kcal mol^{-1} above the boat conformation. It should be noted, however, that the calculations do not take into account properly the hydrogen bonds. Since these hydrogen bonds are likely to contribute mostly to the relative stabilization of the boat and cone conformations, the underestimation of the strength of the hydrogen bonds should result in an overestimation of the steric energies of both conformations. Once this factor is taken into account, it is possible to reconcile the results of the calculations with the experimental result (i.e., exclusive population of the boat conformation).

The calculated structure for the boat conformation of **2** is remarkably similar to the crystallographic conformation determined for **2**·DMF (Table S1 in the supplementary material). The main difference between the experimental and calculated structures is in the O···O nonbonded distances which are overestimated by the calculations by 0.3–0.4 Å possibly due to the partial neglect of the hydrogen bonds.

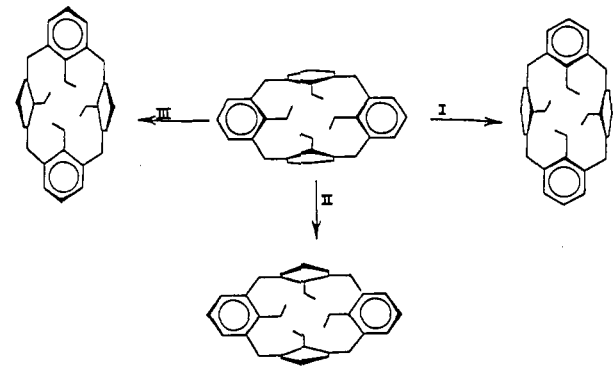
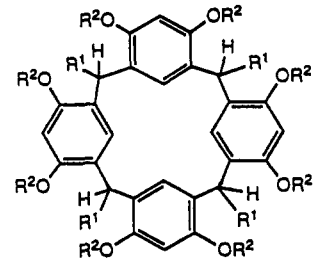


Figure 1. Possible homomerization pathways for calixarene **2**. Methyl gruops are omitted for clarity.

Dynamic Stereochemistry of 2. Due to the lower ideal symmetry of the boat conformation of **2** (C_{2v} symmetry) as compared with **1** (C_{4v} symmetry), several homomerization pathways of the macrocyclic skeleton are possible for **2** whereas for **1** only the inversion process need to be considered. The stereodynamics of the all-cis stereoisomer of resorcinol-based calixarenes **4** which according to the X-ray analysis also exist in a boat conformation[11] have been analyzed by Högberg.[2,12]



a R^1 = Me, R^2 = COC_2H_5
b R^1 = C_6H_{13}, R^2 = COC_2H_5

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Three processes can be considered for the dynamic process operating for **2**. In the first process (I in Figure 1) there is an exchange between the "perpendicular" and "coplanar" rings without including the passage of the OH groups through the macrocyclic cavity. This process does not exchange the "axial" and "equatorial" methylene protons. In the idealized transition state a cone conformation of C_{4v} symmetry is obtained. Since the result of this dynamic process is that the molecule looks as if it was rotated by 90°, this process is called pseudorotation.[13,14] The second process (ii) involves the passage of the rings through the molecular cavity (a ring-inversion process)[13] and keeps the identity of the rings ("perpendicular" or "coplanar") unchanged. The third process (iii) can be formally considered a combination of processes i and ii and

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(12) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046.
(13) Anet, F. A. L. *Top. Curr. Chem.* **1974**, *45*, 169.
(14) It should be noted that in the initial report on the ring inversion barrier of a calix[4]arene (Happel, G.; Mathiasch, B.; Kämmerer, H. *Makromol. Chem.* **1975**, *176*, 3317) the ring inversion process was (incorrectly) dubbed "pseudorotation".

Table I. Coalescence Data for 2

solvent	region	$\Delta\nu$ (Hz)	T_c (K)	$\Delta G_c^{\ddagger}$ (kcal mol^{-1})
1:1 CD_2Cl_2–$CDCl_3$	CH_2	15.3[a]	214	10.9
1:1 CD_2Cl_2–$CDCl_3$	CH_3	71.8[b]	223.5	10.7
pyridine-d_5	CH_3	183[b]	257	11.8

[a] The experiment was conducted on a 500-MHz instrument. [b] The experiment was conducted on a 200-MHz instrument.

involves the passage of the rings through the molecular cavity but with concomitant exchange of the perpendicular and parallel rings. Both processes ii and iii exchange the "axial" and "equatorial" methylene protons. The three processes are depicted in Figure 1.

What is the process of lowest activation energy (threshold mechanism) for **2**? In contrast to the resorcinol aldehyde condensation products studied to date, the uniqueness of **2** is that two probes are available: the two unequivalent rings and the diastereotopic methylene protons. In principle it should be possible to distinguish between the different processes by comparing the barriers measured from the exchange between the "perpendicular" and "parallel" rings ($\Delta G^{\ddagger}_{Ph}$)(measured either from the coalescence of the OH, aromatic protons, or methyl groups) and the barrier for the exchange of the diastereotopic methylene protons ($\Delta G^{\ddagger}_{AB}$). If the values of $\Delta G^{\ddagger}_{Ph}$ and $\Delta G^{\ddagger}_{AB}$ are identical, this will indicate that the threshold mechanism is iii, whereas if $\Delta G^{\ddagger}_{Ph} < \Delta G^{\ddagger}_{AB}$ or $\Delta G^{\ddagger}_{Ph} > \Delta G^{\ddagger}_{AB}$ this will indicate that the threshold mechanism is either i or ii.

Raising the temperature of a solution of **2** results in the pairwise coalescence of the methylene, methyl, aromatic, and OH protons (Figure 2). From the frequency difference between methyl groups under slow exchange (71.8 Hz) and the coalescence temperature (214 K), a barrier of 10.7 kcal mol^{-1} was calculated for the exchange process.[15] Due to the small separation between the resonances arising from the two methylene protons we measured the coalescence of the protons on a 500-MHz instrument. The results of the coalescence experiment are collected in Table I, which shows that *the barriers for the exchange of the methyl and methylene protons are identical within experimental error* (10.7 and 10.9 kcal mol^{-1} respectively). This result indicates that the threshold rotational mechanism for **2** corresponds to a ring inversion, which in addition to exchanging the "perpendicular" and "coplanar" rings exchanges between the diastereotopic methylene protons. In a molecular dynamics study Reinhoudt and co-workers concluded that the conformational inversion pathway of the cone conformation of **1** involves the stepwise passage of the phenolic rings through the ring annulus, with the partial cone and 1,2- or 1,3-alternate conformations as intermediates in the inversion pathway.[16] The DNMR results are in agreement with an inversion process having a symmetric intermediate in which the "perpendicular" and "coplanar" rings are symmetry equivalent (i.e., the 1,2- or 1,3-alternate conformations) since in these cases the inversion process should result also in interconversion between the "perpendicular" and "coplanar" rings. The DNMR data excludes a one-step inversion process which retains the identity of the rings.

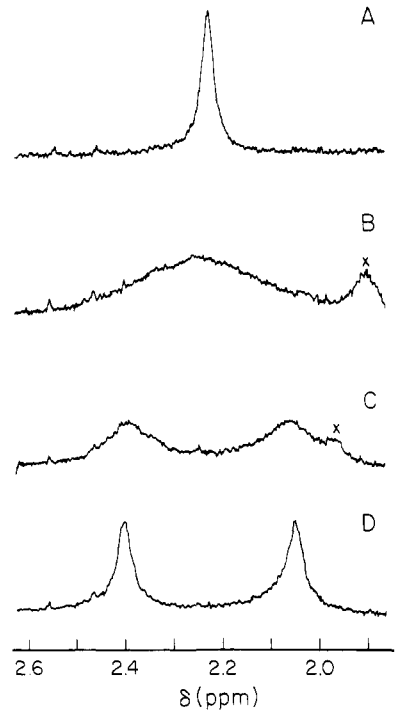

Figure 2. ^{1}H 200-MHz NMR spectrum of the methyl region of **2** in 1:1 $CDCl_3$–CD_2Cl_2 at different temperatures: A, at 210 K; B, at 218 K; C, at 224 K; D, at 246 K.

The pseudorotation process (i) must be of higher energy, in agreement with the molecular mechanics calculations that predict that the "cone" conformation (the presumed transition state for the pseudorotation) lies 31.2 kcal mol^{-1} above the boat conformation.

Comparison between 2 and the Resorcinol-Derived Systems. The all-cis resorcinol-derived calixarenes **4** differ from **2** in several aspects. Since substituents are present at the benzhydrilic position of **4** only process i results in homomerization while processes ii and iii result in diastereomerization (i.e., relocation of the substituents from axial to equatorial positions). For the all-cis calixarenes **4** studied only a single species was detected by NMR.[11,17] This could be either the result of a fast inversion process at room temperature[17d] or the result of a strong conformational bias. For these calixarenes the DNMR data indicate that the pseudorotation process is operating. Since only a single conformer was detected, only the pseudorotation process could be followed by NMR. It is not clear therefore whether the pseudorotation process indeed corresponds to the threshold mechanism of **4**.

Restricted Rotation about the Alkyl–Macrocyclic Bonds in the Resorcinol-Derived Calixarenes. A dynamic process present exclusively in system **4** is rotation about the alkyl or aryl groups attached to the methine carbons. Two claims have been reported on the detection of restricted rotation of alkyl groups attached to the methine carbons in these systems. Rather surprisingly, both claims seem to imply that the barrier of rotation about the CH–alkyl bond in these systems is abnormally high. Högberg[17a] reported that the methyl signals of **4a** broadened by cooling a sample to 241 K in the ^{1}H NMR spectrum. This process was ascribed to the slowing of the rotation of the methyl groups. It could be possible that

(15) For calculating the rate of exchange at the coalescence temperature (k_c) we used the Gutowsky–Holm equation ($k_c = \pi\Delta\nu/\sqrt{2}$): Gutowsky, H. S.; Holm, H. C. *J. Chem. Phys.* **1956**, *25*, 1228).

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the process observed corresponds to freezing the ring inversion and not to the methyl rotation since the barrier of rotation of sterically unencumbered methyl group is very low. It has been claimed that the appearance of the benzhydrilic methine protons in a cis-trans-cis resorcinol heptanal octaacetyl derivative **4b** as a doublet of doublets by coupling with CH_2 is due to hindered rotation of the hexyl groups.[17b] The spectrum was unchanged when the sample was heated to 120 °C. An alternative explanation for the appearance of the spectrum is that, since the protons of the CH_2 unit attached to the macrocyclic ring are symmetry nonequivalent (no conformation exists in which a mirror plane bisects the CH_2 unit) they are diastereotopic *on any time scale*, even under fast alkyl-ring rotation. These diastereotopic protons are expected to be not only anisochronous but also anisogamous. Consequently, they should differ in their coupling constant to a third proton. It is clear therefore that, provided that their coupling constants to the methine proton are different, the methine proton should appear as a doublet of doublets, as reported by Abis et al.,[17b] and there is no need to invoke restricted rotation about the alkyl–macrocyclic bonds.

Solvent Effect on the Inversion Barrier of 2. The inversion barrier of several calix[4]arenes is solvent dependent. Most notably, changing the solvent from $CHCl_3$ to pyridine-d_5 usually reduces the inversion barrier. For example, the inversion barriers for *p-tert*-butyl-, *p*-H-, *p*-cyclohexyl, and *p-tert*-octylcalix[4]arene are 15.7, 14.9, 15.3, and 14.6 kcal mol^{-1} in $CDCl_3$ and 13.7, 11.8, 12.8 and 12.4 kcal mol^{-1} in pyridine-d_5.[18] The energy reduction in the barrier by the change in solvent for these molecules is about 2.0–2.9 kcal mol^{-1} and has been ascribed to the disruption in the intramolecular hydrogen bonds[18] which are contributing factors to the rigidity of the calixarene. Since calixarene **2** has weaker intramolecular hydrogen bonds that **1** as evidenced by the IR and NMR data, it was of interest to see whether a change of solvent from $CDCl_3$ to pyridine will result in a decrease of similar magnitude in the inversion barrier. As shown by the NMR data (Table I) the use of pyridine as solvent results in an *increase* in the inversion barrier. One possibility for explaining this result is that the pyridine molecules form an endo calix complex with **2**. This complex must be disrupted during the inversion pathway, resulting in an increase of the inversion barrier. Recrystallization of **2** from pyridine resulted, as shown by NMR, in a 1:1 complex of **2** with pyridine. In order to determine whether this is indeed an endo calix complex as suggested by the dynamic NMR data we grew a single crystal of **2**·pyridine and submitted it to X-ray diffraction.

X-ray Diffraction of 2·Pyridine. We have described in our preliminary communication the X-ray structure of **2**·DMF.[5] The DMF molecule which is hydrogen bonded to one of the OH groups is not located inside the molecular cavity but between the molecules. The X-ray data of **2**·pyridine indicate that **2** exists in a boat conformation and that the pyridine molecule is partially included in the cavity of the calixarene molecule. The pyridine molecule showed orientational disorder and therefore the nitrogen atom could not be located. A stereoscopic picture of the complex is shown in Figure 3. Bond lengths and angles and positional parameters are deposited as supplementary material (Tables S2–S4). In general, the conformation of the calixarene ring is similar to the one found for **2**·DMF,

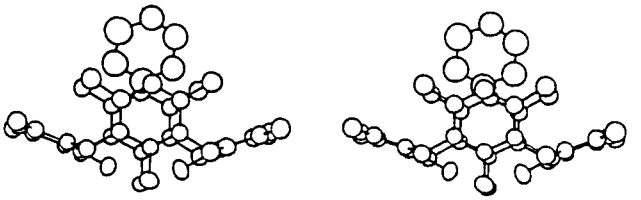
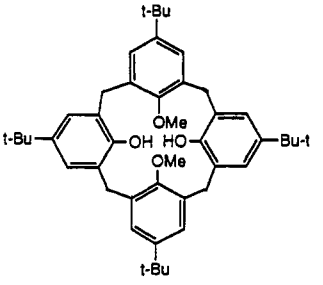


Figure 3. Stereoview of the crystal structure of **2**·pyridine.

which indicates that conformational changes as a result of complexation are minimal. The dihedral angles between the plane defined by the four methylenic carbons and the perpendicular rings are 71.2° and 69.2°, and the angles with the coplanar rings are 21.6° and 25.6°. The capability of **2** of forming endo calix solid-state complexes is of interest since it has been hypothesized that the solid-state endo calix complexes of the parent **1** with aromatic guests are the result of attractive interactions between the π cloud of the guest and the methyls of the *p-tert*-butyl groups (a CH_3–π interaction).[19] In the case of **2** no CH_3–π interaction is possible, since the meta methyl groups are too far away to interact with the pyridine π cloud (cf. Figure 3). It seems possible that π–π interactions are at least partially responsible for the formation of the solid-state endo calix complex.

Fixation of the Boat Conformation. One of the common methods for fixation of the cone conformation (i.e., increasing the barrier to ring inversion) is by replacement of the hydroxylic protons by bulky groups. The 1,3-dimethyl derivative of *p-tert*-butylcalix[4]arene (**5**) exists in a "flattened cone" (boat) conformation.[16,20] In order to prepare the dimethyl ether derivative of **2** we reacted the calixarene with dimethyl sulfate and 20% aqueous NaOH in the presence of a phase transfer catalyst. The dimethyl ether **6** was obtained in 37% yield.



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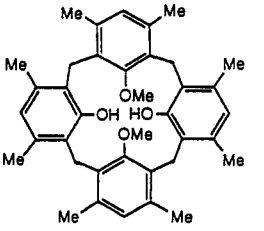

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Calixarene **6** displays in the ^1H NMR spectrum (200 MHz, $CDCl_3$, rt) two methyl (δ = 1.69 and 2.38), two aromatic (δ = 6.51, 6.31), one OH (δ = 5.25 ppm), and one OMe (δ = 3.8) signals and an AB quartet (δ = 3.6, 4.1) for the methylene protons. The anisochrony of the methylene protons in the spectrum is in agreement with a frozen boat conformation in which the two OMe groups are located at distal (nonvicinal) rings. Lowering the temperature to 213 K did not lead to any change in the ^1H NMR spectrum. The ^{13}C NMR spectrum (50 MHz, $CDCl_3$, rt) is also in full agreement with a boat conformation in solution. Two methyl signals (δ = 18.7, 20.1) and single methylene and methoxy carbon signals are observed, in addition to eight signals for the aromatic carbons. It should be noted that dialkylation of a boat conformation at distal hydroxyls should result in two diastereomeric forms, one with the alkoxy groups located at the perpendicular rings and the second form with the groups located in the coplanar rings.

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The NMR data at room temperature indicate that either a fast pseudorotation process takes place which averages the signals of the two diastereomers and results in two residual[21] diastereotopic signals for the methylene protons or the presence of a single conformation. Since the pseudorotation barrier of **6** should be of similar magnitude as that of the barrier of **2**, and the calculations predict that the barrier of pseudorotation is appreciable, we believe that a single frozen conformation is observed.

Crystal Structure of 6. In order to see whether the boat conformation present in **2** is retained in **6**, a single crystal of **6** was grown from 1,2-dimethoxyethane and submitted to X-ray diffraction. Lists of bond lengths and angles and positional parameters (Tables S5–S7) are deposited as supplementary material. The crystallographic data show that the molecule exists in a boat conformation and that the substitution occurred at distal positions. Distal substitution is the usual outcome of the disubstitution of the OH groups in calix[4]arenes.[22] Most notably, the dihedral angles between the plane defined by the four methylene carbons and the plane of the perpendicular rings is 89.4° and 90.5° (the corresponding values for **2** are 72.9° and 73.0°) and the dihedral angles with the coplanar rings are 17.4° and 18.8°. Only one nonbonded O···O distance is within the range of a hydrogen bond (2.7 (1) Å). The two methoxy groups are located at the perpendicular rings and have their methyl groups pointing away from the molecular cavity. An identical orientation was found in the crystal structure of **5**.[16]

Estimation of the Inversion Barrier of 6. The inversion barrier for **6** can be obtained in principle from the coalescence of the methylene protons. However, no broadening of the methylene signals was observed in the ^{1}H NMR spectrum of **6** (200 MHz, $NO_2C_6D_5$) even when the temperature was raised to 414 K. We therefore, decided to resort to the saturation transfer technique,[23] which has been proved useful in the past for measuring high barriers.[24] The experiment was conducted at 414 K by delivering a selective 180° pulse to the low-field methylene doublet followed by a nonselective 180° pulse after a time delay which was varied progressively. No reduction of intensity was observed from the other methylene doublet and from the experiment a T_1 value of 0.83 s was measured for the low-field doublet. Since the relaxation rate ($1/T_1$ = 1.23 s^{-1}) must be faster than the exchange rate between the two protons, the exchange rate between the two sites must be slower than 1.23 s^{-1}. By introducing this value and the temperature of the experiment into the Eyring equation a lower limit of 24.3 kcal mol^{-1} can be estimated for the inversion barrier. It is interesting to note that replacement in **2** of two distal hydroxylic protons by methyls raises the inversion barrier by >13.6 kcal mol^{-1}.

Conclusions

From the identity in the measured barriers for the coalescence of the diastereotopic methylene protons and the coalescence of the methyl signals it is concluded that the dynamic pathway observed for **2** by NMR corresponds to a ring-inversion process which exchanges both the methylene protons and the symmetry nonequivalent "perpendicular" and "coplanar" aryl rings. Changing the solvent from $CDCl_3$ to pyridine-d_5 raises the inversion barrier of **2** due to the presence of an endo calix complex. Dimethylation of **2** results in the fixation of the boat conformation.

Table II. Summary of X-ray Diffraction Data

compd	2	6
formula	$C_{36}H_{40}O_4 \cdot C_5H_5N$	$C_{38}H_{44}O_4$
space group	$P2/n$	$C2/c$
a (Å)	11.686	31.527
b (Å)	26.397	12.041
c (Å)	10.696	17.916
β	90.19	114.78
V (Å^3)	3299 (1)	6175
ρ_{calc} (g cm^{-3})	1.24	1.22
Z	4	8
μ (Mo Kα) (cm^{-1})	0.43	0.42
no. of unique reflections	4424	3921
no. of reflections with $I \geq 2s(I)$	2228	2621
R	0.104	0.073

Experimental Section

Crystallography. Data were measured on a PW 1100/20 Philips four circle computer-controlled diffractometer. Intensities were corrected for Lorentz and polarization effects. All nonhydrogens atoms were located by using the results of the SHELXS-86 direct method analysis.[25] All carbon atoms were refined isotropically. After several cycles of refinements the positions of the hydrogens atoms were calculated and added with a constant isotropic temperature factor of 0.05 Å^2 to the refinement process. A summary of the X-ray data is collected in Table II. Atomic coordinates, bond lengths, and angles are deposited as supplementary material.

2,6-Dimethyl-4-hydroxybenzyl Alcohol. The compound was prepared by reaction of a formaldehyde solution and 3,5-xylenol according to the procedure of ref 26 (yield 27%, lit. 50%) mp 166 °C (lit. mp 170–171 °C): ^{1}H NMR ($CDCl_3$) δ 2.38 (CH_3, 6 H), 4.67 (CH_2, 2 H), 6.53 (2 H, Ar-H).

2,4-Dimethyl-6-hydroxybenzyl Alcohol. The compound was prepared by $LiAlH_4$ reduction of the corresponding diacetate according to the literature procedure[27] (yield 30%, lit. 8%): mp 88 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (3 H, Me), 2.46 (3 H, Me), 4.91 (2 H, CH_2), 6.54 (1 H, Ar-H), 6.56 (1 H, Ar-H), 7.26 (OH); ^{13}C NMR ($CDCl_3$) δ 18.97 (Me), 20.94 (Me), 60.09 (CH_2), 114.89, 119.99, 123.09, 138.72, 155.99 (6 aromatic C).

4,6,10,12,16,18,22,24-Octamethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecene-25,26,27,28-tetrol (2). To a solution of 2,4-dimethyl-6-hydroxybenzyl alcohol (0.2 g, 1.3 mmol) in 22 mL of $C_6H_5NO_2$ at 90 °C was added 0.11 g of $AlCl_3$, and the mixture was stirred at room temperature for 1 h. After the reaction mixture was poured on water, the phases were separated, and the organic phase was filtered through a sintered glass funnel (no. 3). The filtrate was washed twice with water, and the organic phase was dried ($MgSO_4$). Evaporation of the solvent under low pressure yielded 94.1 mg (54%) of **2**. Recrystallization from DMF or pyridine afforded **2**·DMF or **2**·pyridine, respectively. A solvent-free sample could be obtained by sublimation under reduced pressure: mp 330–332 °C; ^{1}H NMR ($CDCl_3$, rt) δ 2.25 (s, Me, 24 H), 3.38 (s, CH_2, 8 H), 6.51 (s, Ar-H, 4 H), 8.19 (s, OH, 4 H); IR ν_{OH} = 3290 cm^{-1}, UV ($CHCl_3$) ϵ = 2749 (λ_{max} = 280 nm); MS (EI, 70 eV) m/z 536 (M, 36), 135 (M – 2,3,5-$Me_3C_6H_2OH$-H, B). Anal. Calcd for $C_{36}H_{40}O_4$: C, 80.56; H, 7.51. Found: C, 80.70; H, 7.38.

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26,28-Dimethoxy-4,6,10,12,16,18,22,24-octamethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecene-25,27-diol (6). To a solution of 0.421 g (0.746 mmol) of **2** in 300 mL CH_2Cl_2 were added 10 mL of a solution of NaOH (10%), 1.8 mL of dimethyl sulfate, and 0.4 g (1.24 mmol) of tetrabutylammonium bromide. The mixture was refluxed overnight with stirring. The phases were separated, and to the organic phase was added a dilute solution of ammonium hydroxide. The phases were separated, and the organic phase was washed once with water and dried. Recrystallization of the residue from 1,2-dimethoxyethane afforded 0.165 g of **6** (37%): mp 330 °C dec; ^{1}H NMR ($CDCl_3$, rt) δ 1.69 (s, CH_3, 12 H), 2.38 (s, CH_3, 12 H), 3.56 (d, J = 15.2 Hz, CH_2, 4 H), 3.74 (s, OCH_3, 6 H), 4.15 (d, J = 15.2 Hz, CH_2, 4 H), 5.25 (s, OH, 2 H), 6.31 (s, Ar-H, 2 H), 6.51 (s, Ar-H, 2 H); ^{13}C NMR ($CDCl_3$, rt) δ 18.70, 20.10, 24.62, 62.36 (OMe), 122.85, 123.95, 128.88, 129.12, 134.17, 135.62, 154.19, 156.66; UV ($CHCl_3$) ϵ = 3148 (λ_{max} = 280 nm); MS m/z 564 (M, 15.8), 147 (B, 100), 91 (41); IR ν OH = 3540 cm^{-1}. Anal. Calcd for $C_{38}H_{44}O_4$: C, 80.82; H, 7.85. Found: C, 80.66; H, 7.95.

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Registry No. **2**, 123775-99-5; **2**·pyridine, 137172-87-3; **6**, 137122-95-3; 2,4-dimethyl-6-hydroxybenzyl alcohol, 67730-49-8; 2,6-dimethyl-4-hydroxylbenzyl alcohol, 28636-93-3.

Supplementary Material Available: Figures S1 and S2 (numbering scheme for **2**·pyridine and **6**), Table S1 (calculated and experimental parameters for the boat foam), and Tables S2-S7 (bond lengths and angles and positional parameters for **2**·pyridine and **6**) (10 pages). Ordering information is given on any current masthead page.

Per-3,6-anhydro-α-cyclodextrin and Per-3,6-anhydro-β-cyclodextrin[1]

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The synthesis of the per-3,6-anhydro derivatives of α- and β-cyclodextrins (CDs) is described starting from the corresponding per-6-tosylates. These could only be obtained as pure compounds following repeated HPLC under reversed-phase conditions of the crude products isolated after tosylation of α-CD and β-CD in pyridine with *p*-toluenesulfonyl chloride. Treatment of the per-6-*O*-tosyl-α- and β-CDs with warm aqueous sodium hydroxide solutions (50-60 °C) afforded the per-3,6-anhydro-α- and β-CDs in good yields. The development of an alternative and successful strategy for the synthesis of per-3,6-anhydro-α-CD from the known per-2,3-di-*O*-benzoyl-6-*O*-tosyl-α-CD relies upon the use of triethylamine as base in refluxing aqueous methanol. The per-3,6-anhydro-CDs have been fully characterized by FABMS and NMR spectroscopy. Their specific optical rotations, which are solvent dependent, confirm the chiral nature of these molecules. The anhydrides are soluble in such widely different solvents as dichloromethane and water. There is evidence from FABMS that per-3,6-anhydro-α-CD forms a complex with the triethylammonium cation while per-3,6-anhydro-β-CD solubilizes nitrobenzene in deuterium oxide solutions.

Introduction

In the 100 years since they were first isolated, but especially during the last 25 years, cyclodextrins have been the subject of much detailed investigation.[2] It is now well established[3] that these cyclic oligosaccharides, which are composed of α(1-4) linked D-(+)-glucopyranose units, have the overall molecular shape of a truncated cone. The most characteristic aspect of their chemistry is their ability to form inclusion complexes with a wide variety of substrates. As a result, they have been investigated extensively as enzyme mimics,[4] as well as finding varied applications in chemical technology.[5]

Many research workers have sought to modify the binding properties and catalytic behavior of cyclodextrins through their chemical modification.[6] Unfortunately, because of problems associated with their chemoselective and regioselective functionalization and the subsequent purification of the derivatives, many reports have appeared that include highly exaggerated claims of selectivities operating in reactions and of the purities of the CD derivatives isolated. Although these problems were addressed a number of years ago in an excellent paper by Lehn,[7] the standards that were set by this research are still not being practiced universally.

The vast majority of the well-characterized derivatives that have been isolated have structures very similar to those of the parent compounds.[6] It has been our aim to synthesize CD derivatives whose gross structures differ significantly from those of the parent compounds. Such derivatizations of CDs would be expected to have a pro-

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