Totally and Partially Saturated Calixarene Analogues

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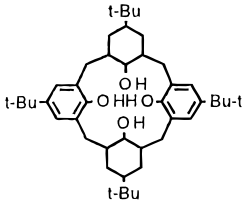
Abstract: Catalytic hydrogenation (Pd/C) of calix[4]arene afforded derivatives in which one (**6a**), two distal (**7f**) or all phenols (**11** and **13d**) have been hydrogenated. **6a** adopts a conformation in which the phenol groups are oriented syn and the cyclohexanol (with an axial OH group) exists in an anti-down arrangement. The cyclohexanol rings of **7f** adopt an anti-down/gauche-down conformation and both the equatorial and axial cyclohexanol OH groups are involved in hydrogen bonding. The configuration of the perhydroxanthene subunits of the saturated diether **11** is *cis-syn-cis* with all C−O bonds located in axial positions of the cyclohexyl rings. In the saturated metacyclophane **13d** pairs of methine hydrogens at the four rings are arranged alternately above and below the mean macrocyclic plane. Calculations with the MM3 program indicate that **6a** and **13d** are the lowest energy isomers.

Introduction

The cyclodextrins are one of the most thoroughly investigated molecular hosts.[1] In these systems several six-membered sugar units are arranged along a macrocycle and delimit a molecular cavity. A class of compounds which has not received much attention are [1_n]-metacyclophanes derivatives incorporating cyclohexanol rings in the macrocyclic skeleton (e.g., **1**).[2,3] The macrocyclic compound **1** is in principle synthetically amenable by the hydrogenation of *p-tert*-butylcalix[4]arene (**2**).[4] The saturated calixarenes are of interest both as potential synthetic intermediates for the preparation of functionalized calixarenes, and per se, as novel host systems.



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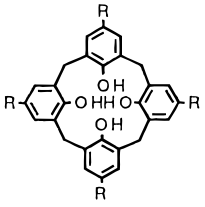
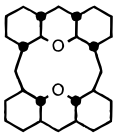


2 R = *t*-Bu
3 R = H



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A large number of isomers are possible for **1** due to the presence of several stereocenters. In addition to the orientation of the aromatic rings, several factors should be taken into consideration for the conformational characterization of a given isomer: (i) The conformation (chair or twist) of the saturated rings. (ii) The location of the bridging methylene groups and the OH in the saturated rings (e.g., equatorial or axial). (iii) The conformation adopted along the cyclohexyl−CH_2 bonds (i.e., gauche or anti).

In this article we describe the preparation of partially and totally saturated calix[4]arenes derivatives and analyze the configurational isomerism and conformation of the systems.

Results and Discussion

Substrate for the Hydrogenation. The choice of **3** as the substrate for the hydrogenation rather than the parent *p-tert*-butylcalix[4]arene (**2**) was based on two considerations: (i) The phenol rings in **3** are more sterically accessible than in **2**, thus a more facile hydrogenation was expected. (ii) Because 16 stereocenters are present in the hydrogenation products of **2** (the methine carbons), if the reaction proceeds without any stereoselectivity, a very complex stereoisomeric mixture might be obtained. The use of the de-*tert*-butylated calix[4]arene **3** was expected to render the product analysis somewhat more manageable because the number of stereocenters in the totally hydrogenated product is reduced to 12.

Preparation of Hexahydro- and Dodecahydrocalixarene Derivatives. Attempts to hydrogenate **3** under drastic conditions (1450 psi H_2, Raney Ni/240 °C) afforded the diether **4**,[5] which suggests that a tetracyclohexanol derivative is probably formed, but subsequently undergoes intramolecular dehydration. We decided to attempt the hydrogenation using Pd/C which proved successful in the hydrogenation of several polyphenyl benzenes.[6] In parallel to our studies, Harrowfield and co-workers[7] performed the hydrogenation of **3** with $RhCl_3 \cdot 3H_2O$[8] which afforded the calixketone **5** as the main product (eq 1).[7a]

The preparation of partially saturated calix[4]arenes analogues was achieved by halting the hydrogenation of **3** (600 psi H_2, Pd/C, 100 °C) before completion. This afforded a mixture of

(1) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978.

(2) For recent reviews on the conformation of cyclohexyl rings, see: (a) *Conformational Behavior of Six Membered Rings*; Juaristi, E., Ed.; VCH Publishers: New York, 1995. (b) Mann, G. *Z. Chem.* **1990**, *30*, 1. (c) Anderson, J. E. In *The Chemistry of Alkanes and Cycloalkanes*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1992, Chapter 3. (d) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(3) For a recent example of a paracyclophane incorporating a cyclohexyl ring, see: Yang, F.-M.; Lin, S.-T. *J. Org. Chem.* **1997**, *62*, 2727.

(4) For reviews on calixarenes, see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (d) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1.

(5) Grynszpan, F.; Biali, S. E. *Chem. Commun.* **1996**, 195.

(6) For example, see: Columbus, I.; Hoffman, R. E.; Biali, S. E. *J. Am. Chem. Soc.* **1996**, *118*, 6890.

(7) (a) Bilyk, A.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *An. Quim. Int. Ed.* **1997**, *93*, 363. (b) Bilyk, A.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1997**, 4251.

(8) Azran, J.; Buchman, O.; Amer, I.; Blum, J. *J. Mol. Catal.* **1986**, *34*, 229.

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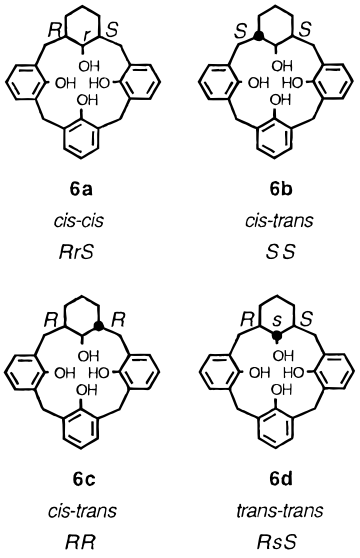
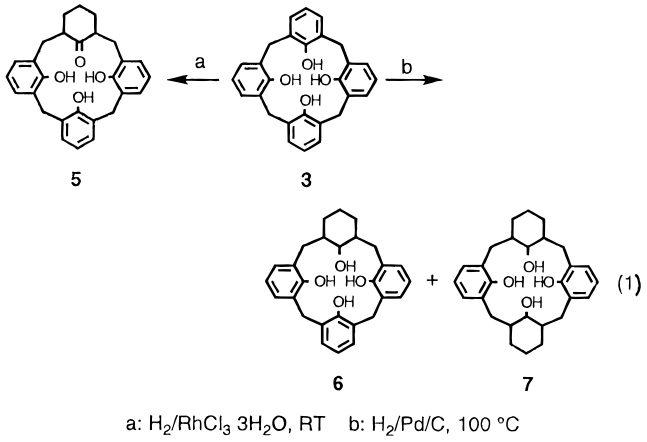
Scheme 1



starting material, and hexahydro- and the distal (1,3)-dodecahydrocalix[4]arene derivatives **6** and **7** (eq 1).



Hexahydrocalix[4]arene derivative. (a) Isomerism. Four configurational isomers are possible for **6** (Scheme 1). The *cis-trans* isomers **6b** (*SS)* and **6c** (*RR*) represent enantiomers, and the *all-cis* and *all-trans* forms **6a** (*RrS*) and **6d** (*RsS)* are achiral *meso* forms.[9] In general, the chair form is the lowest energy conformation of a cyclohexyl ring, and in this form an equatorial disposition of an alkyl substituent is of lower energy than that in an axial disposition.[10] On this basis, the *meso* forms **6a** and **6d** are expected to be energetically preferred over the enantiomeric pair **6b**/**6c** because only in the *meso* forms are a diequatorial arrangement of the cyclohexyl-CH_2 bonds possible. Harrowfield and co-workers obtained by $NaBH_4$ reduction of **5**, a mixture of **6a** and **6d** (the major product), and both products were characterized by X-ray crystallography.[7b]

Conformation. By analogy to *intra*annular monosubstituted calix[4]arene derivatives, it is highly likely that the three phenol rings of **6a** and **6d** prefer a syn arrangement (the three rings identically oriented "above" or "below" the mean macrocyclic plane) in order to allow for intramolecular hydrogen bonds. In principle, the saturated ring can orient its C−OH ("C_α") carbon "up" (toward the calixarene "upper rim",[4] Figure 1) or "down" (toward the "lower rim"). Assuming that only staggered arrangements are adopted along the cyclohexyl-CH_2 bonds, two

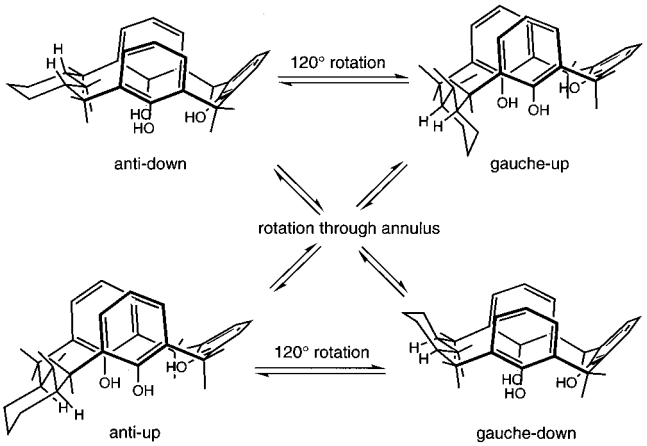


Figure 1. The four staggered conformations of a calixarene derivative in which one phenol ring has been replaced by a cyclohexyl. The phenol rings are assumed to exist in a syn arrangement.

Table 1. Calculated (MM3) Relative Steric Energies (RSE, in kcal mol^{-1}) of Selected Conformers of Partially Hydrogenated Calixarene Derivatives[a]

compound	configuration	conformation	RSE
6a	*RrS (cis-cis)*	anti-up	6.5
		gauche-down	4.0
		anti-down	0.0
		gauche-up	16.2
6d	*RsS (trans-trans)*	anti-up	8.5
		gauche-down	0.9
		anti-down	2.8
		gauche-up	17.4
7a	*RrS/RrS (cis-cis/cis-cis)*	gauche-down/gauche-down	10.8
		anti-down/gauche-up	17.2
		anti-down/anti-down	0.0
7c	*RrS/RsS*	gauche-up/gauche-up	7.5
	(cis-cis/trans-trans)	anti-up/gauche-up	13.6
		gauche-up/anti-up	15.6
		anti-down/anti-down	6.8
7f	*RrS/SsR*	gauche-up/gauche-down	20.5
	(cis-cis/trans-trans)	anti-down/gauche-down	1.4
		gauche-down/anti-down	8.8
		anti-down/anti-up	10.0
7h	*RrS/SrR*	gauche-up/gauche-down	28.2
	(cis-cis/cis-cis)	anti-down/gauche-down	7.7
		anti-down/anti-up	7.8
7p	*RsS/RsS*	gauche-down/gauche-down	1.9
	(trans-trans/trans-trans)	anti-up/gauche-down	12.2
		anti-down/anti-down	7.0
7r	*RsS/SsR*	gauche-up/gauche-down	18.0
	(trans-trans/trans-trans)	anti-down/gauche-up	5.7
		anti-up/anti-down	12.9
8	*RS (cis)*	anti-up	2.2
		gauche-down	0.2
		anti-down	0.0
		gauche-up	10.9
10a	*RS/RS (cis/cis)*	gauche-down/gauche-down	2.9
		anti-down/gauche-up	7.1
		anti-down/anti-down	0.0
10b	*RS/SR (cis/cis)*	gauche-up/gauche-down	17.1
		anti-down/gauche-down	1.7
		anti-down/anti-up	2.7

[a] Energies of **6**, **7**, **8**, and **10** are relative to the lowest energy form of each compound (e.g., the anti-down conformer of **6a** for **6**).

(9) Because the alcohol carbon in **6a** and **6d** qualifies as a pseudoasymmetric center (i.e., a stereogenic nonchirotopic atom), its configuration is described with a lowercase letter (Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Eng.* **1966**, *6*, 385). See also: Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 6, 3319.

(10) For exceptions to these rules, see: (a) Golan, O.; Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 9300. (b) Biali, S. E. *J. Org. Chem.* **1992**, *57*, 2979. (c) Kang, F.-A.; Yin, C.-L. *J. Am. Chem. Soc.* **1997**, *119*, 8562. (d) Weiser, J.; Golan, O.; Fitjer, L.; Biali, S. E. *J. Org. Chem.* **1996**, *61*, 8277. (e) ref 6.

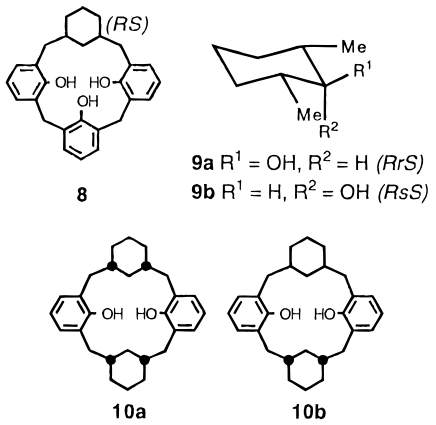
different conformations (gauche and anti)[11] are feasible for either the up or down arrangements. The gauche-down form resembles a cone conformation, and the anti-up and gauche-up forms somewhat resemble a partial cone conformation in which the saturated ring is pointing in the opposite direction to the rest of the rings.

(c) Rotational Processes in 6. A rigid 120° rotation of the cyclohexyl ring along the cyclohexyl−CH_2 bonds interconverts the anti-up ⇄ gauche-down conformers as well as the anti-down ⇄ gauche-up forms. The transition between the two anti (or two gauche) forms requires that all rings rotate through the macrocyclic annulus, in a process analogous to the cone-to-cone inversion in a calixarene (Figure 1).[4] This process does not affect the axial/equatorial dispositions of the groups attached to the cyclohexyl ring, although ring inversion of the cyclohexyl ring modifies the axial/equatorial dispositions of the substituents (including the bridging methylene groups). Neither of these processes can render the protons within a methylene group equivalent, and these remain diastereotopic even if all rotations are fast on the NMR time scale.

(d) Molecular Mechanics Calculations. To assess the intrinsic conformational preferences of a cyclohexyl ring incorporated into a macrocycle, **8** was examined using the MM3 program.[12] The calculations were conducted assuming that the phenol rings are arranged syn and that the cyclohexyl ring is connected to the macrocycle through its equatorial positions. The calculations of **8** (*RS* form) indicate (Table 1) that the lowest energy conformers are the anti-down and gauche-down, with the anti-up and gauche-up conformers lying 2.2 and 10.9 kcal mol^{-1} above the anti-down form, respectively.

Calculations were also conducted for the potential low-energy configurational isomers of **6** and **7**. To facilitate the estimation of the relative stability of the different isomers (e.g., *RrS* and *RsS* for **6**) the calculated energies in Table 1 are relative to the lowest energy configurational isomer of a given compound. As indicated by the calculations on **6a** and **6d** (Table 1), the presence of an *intra*annular OH affects the relative stability of the low-energy "down" forms. In the *RrS* isomer **6a** the anti-down form is 4.0 kcal mol^{-1} lower in energy than the gauche-down conformation, but the relative stability is reversed in the *RsS* isomer **6d**. These preferences can be rationalized, because in the lowest energy conformation of each isomer, the cyclohexyl OH group is oriented roughly parallel to the phenolic hydroxyls. This orientation allows for the presence of a circular array of hydrogen bonds while minimizing repulsive transannular interactions. The X-ray structures of **6a** and **6d** reported by Harrowfield and co-workers[7b] as well as our independent determination of the crystal structure of **6a** (see below) corroborate the computational predictions: **6a** adopts an anti-down conformation and the conformation of **6d** is gauche-down.

The cyclohexanol OH groups of **6a** and **6d** adopt axial and equatorial positions, respectively, with the saturated ring connected to the macrocycle through its equatorial positions. The calculations indicate that the *RrS* form **6a** is 0.9 kcal mol^{-1} lower in steric energy than the *RsS* form **6d** (Table 1), i.e., the axial disposition of the OH group is of lower energy than the equatorial disposition. This is in contrast to the model system **9** for which the *RrS* form **9a** (OH equatorial) is calculated as 2.4 kcal mol^{-1} more stable than the *RsS* isomer **9b**. The stability



reversal found in **6a**/**6d** may be the result of larger transannular steric repulsions when the substituent is equatorial, a more efficient hydrogen bonding array when the OH is axial, or torsional interactions. However, because in both diastereomers rather similar hydrogen bonding arrays seem to be present,[7b] it can be concluded that steric effects are in part responsible for the *RrS*/*RsS* stability reversal in **6**.[13]

(c) Configuration and Solution Conformation. Unaware of Harrowfield parallel efforts, we submitted the isolated hexahydrocalix[4]arene to X-ray diffraction. The crystal data are identical to those reported by Harrowfield and co-workers[7b] for the minor product of the $NaBH_4$ reduction of **5**. Our data indicate that the cyclohexanol moiety possesses an *RrS* configuration (i.e., **6a**), adopts an anti-down arrangement, and that the hydroxyl group is located in an axial position (Figure 2). The four hydroxyl groups are engaged in a circular array of hydrogen bonds, as judged by the O···O nonbonded distances (O2 (ax)···O1: 2.822(2) Å, O1···O4: 2.675(2) Å, O4···O3: 2.661(2) Å, O3···O2: 2.735(2) Å). The crystal conformation is almost identical to the conformation predicted by the MM3 calculations. The product formed in the hydrogenation corresponds to the lowest energy isomer, because from all possible configurational isomers, **6a** possesses the lowest steric energy. The major product obtained by $NaBH_4$ reduction of **5**[7b] corresponds to the less stable epimer. Analysis of the ^1H NMR spectrum of **6a** and **6d** by Bilyk et al. indicated that the solution conformations are similar to those found in the crystal.[7b]

Stereochemistry of Dodecahydrocalix[4]arene 7. (a) Number of Configurational Isomers. Disregarding conformational isomerism, the calculation of the number of possible isomers of **7** of each symmetry can be conveniently performed by the configurational matrix method.[14] For that purpose a one-dimensional configurational matrix consisting of six binary digits is constructed, which describes the configurations of the six stereocenters (Figure 3). Sixty-four matrixes exist, which do not correspond to 64 distinct compounds, since each isomer is represented by more than one matrix. Depending on the

(11) For simplicity, "gauche" and "anti" will denote conformations in which the cyclohexyl methine protons at C-2 and C-6 ("C_β") are oriented gauche/gauche or anti/gauche to the pair of bridging methylene protons, respectively.

(12) Allinger, N. L. MM3 1994 Force Field for UNIX and VAX (updated June 3, 1994).

(13) This is further supported by MM3 calculations on analogues of **6a** and **6d** in which the cyclohexanol OH was replaced by a methyl. Although the methyl substituent is not involved in hydrogen bonds, the isomer with the axial methyl is the lower energy form.

(14) Willem, R.; Pepermans, H.; Hoogzand, C.; Hallenga, K.; Gielen, M. *J. Am. Chem. Soc.* **1981**, *103*, 2297. See also: Biali, S. E.; Buda, A. B.; Mislow, K. *J. Org. Chem.* **1988**, *53*, 1289.

(15) The symmetry number is the number of indistinguishable but nonidentical positions in which the molecule can be turned by rigid rotation. See ref 2d, p 96.

(16) The number of symmetry matrixes is inversely proportional to the symmetry number. See: Brocas, J.; Gielen, M.; Willem, R. *The Permutational Approach to Dynamic Stereochemistry*; McGraw-Hill, New York, 1983, Chapter 8.

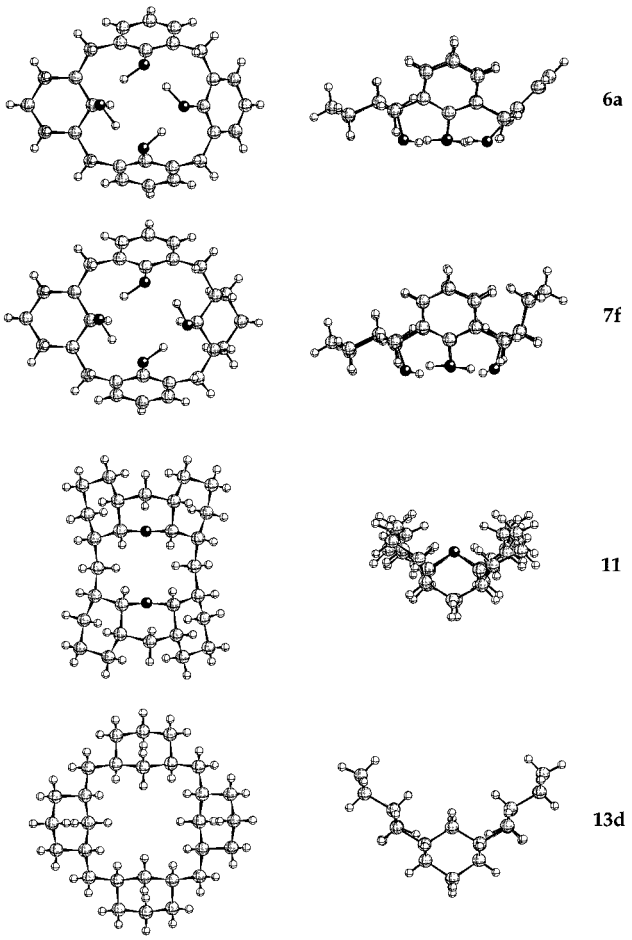


Figure 2. Top and side views of the crystal structures of **6a**, **7f**, **11**, and **13d**.

possible symmetry numbers (σ) ($\sigma = 2$ (C_{2h}, C_{2v}, or C_2) or $\sigma = 1$ (C_s, C_i, or C_1)),[15] a given isomer is represented by either two and four different matrixes, respectively (Figure 4).[16]

Matrixes representing isomers which include a C_2 axis as a symmetry operation must be invariant to that element. These matrixes possess the general form *(ABC ABC*) (if the C_2 axis is collinear with the *z* axis, as in the example shown at the top of Figure 4) or (*ABC (1-C)(1-B)(1-A)*) (for $C_2(x)$) where *A*, *B*, *C* $\in \{1,0\}$. There are 16 matrixes describing structures with a C_2 axis corresponding to 8 configurational isomers. The number of matrixes representing structures of C_s symmetry is $64-16 = 48$, and because isomers with $\sigma = 1$ are represented by 4 matrixes each, this corresponds to 12 isomeric forms. The 20 isomeric forms of **7** are collected in Figure 5. Eight isomers are achiral *meso* forms (**7a**, **7c**, **7f**, **7h**, **7i**, **7l**, **7p**, **7r**) and 12 correspond to 6 enantiomeric pairs (**7b**/**7d**, **7e**/**7g**, **7j**/**7o**, **7k**/**7s**, **7m**/**7q**, and **7n**/**7t**). The 20 isomers can be separated into 10 pairs of compounds (e.g., **7a**−**7h**, **7c**−**7f** and **7p**−**7r**), each pair possessing identical pattern of configurations of the stereocenters (e.g., *RrS* and *RsS* for **7c** and **7f**) but differing in their arrangement along the macrocycle (e.g., *RrS SsR* in **7c**, *RrS RsS* in **7f**).

(b) Conformation. On the basis of the axial/equatorial disposition of the bridging methylene groups, it could be expected that the low-energy isomers of **7** should be **7a**, **7c**, **7f**, **7h**, **7p**, and **7r**, because only in these forms can both cyclohexanols be connected to the macrocycle exclusively through their equatorial positions. In each ring the methine carbons connected to C_α ("C_β") possess opposite configurations, i.e., project their hydrogens in the same direction ("above" or "below" the cyclohexyl mean plane). As exemplified by the analogues **10a** and **10b**, depending on whether the protons at the two pairs of methines are oriented in the same (**10a**) or opposite (**10b**) directions, two different conformational behaviors should be observed (Figure 6). By analogy to **6**, it could be expected that the potential low-energy conformations of the saturated rings will be anti-down/anti-down and gauche-down/gauche-down for **10a**, and for **10b** the preferred conformation should be anti-down/gauche-down. Rotation through the annulus interconverts the anti-down with the gauche-down conformation. However, because the process requires the rotation of all rings, the conformation of both saturated rings must change simultaneously, and single-ring interconversions of the type anti-down/anti-down $\rightleftarrows$ anti-down/gauche-down are precluded for **10a** and **10b**. There is no conformational restriction for a 120° rotation of a single ring (e.g., an anti-down/anti-down $\rightleftarrows$ gauche-up/anti-down interconversion for **10a**).

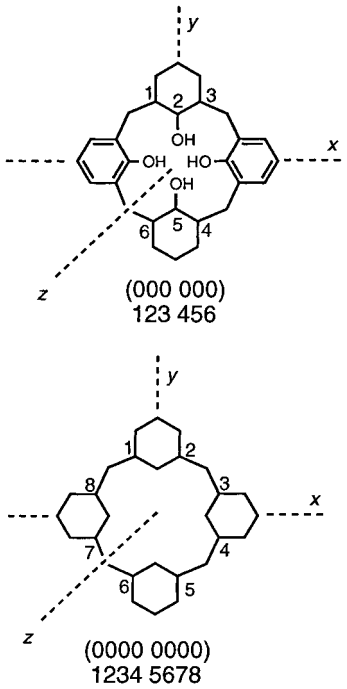


Figure 3. Convention used for the configurational description of the isomers of **7** (left) and **13** (right). The molecules are oriented in the paper (*xy*) plane. The binary digits "1" and "0" denote that the hydrogens on the stereocenters are pointing toward or away from the observer, respectively. The sets of digits in the matrixes describe the configurations of the stereocenters, starting from position 1 and proceeding in a clockwise fashion along the skeleton.

MM3 calculations were performed on the isomers **7a**, **7c**, **7f**, **7h**, **7p**, and **7r**, as well as on their analogues **10a** and **10b** (Table 1). In all cases only a syn arrangement of the phenol rings was considered. The calculations indicate that the preferred conformation of **10a** and **10b** is anti-down/anti-down and anti-down/gauche-down, respectively. The lowest energy isomer is **7a** (which adopts an anti-down/anti-down conformation), with **7f** (*RrS* anti-down/*SsR* gauche-down) and **7p** (gauche-down/gauche-down) lying 1.4 and 1.9 kcal mol^{-1}, respectively, above it. The two axial OH groups of **7a** and the axial and equatorial OH groups of **7f** participate, together with the phenolic hydroxyls, in a circular array of hydrogen bonds.

The forms **7h** and **7r** lie 7.7 and 5.7 kcal mol^{-1}, respectively, above **7a**. Although (as shown by **10b**) the intrinsic preferred conformation of the saturated rings is anti-down/gauche-down, in this conformation one cyclohexanol OH group is forced into the cavity center. The steric destabilization is so large that in

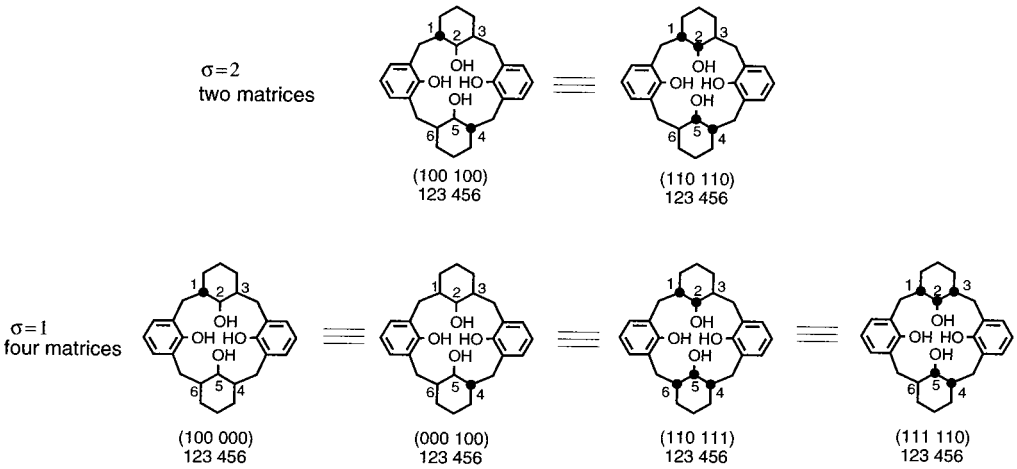


Figure 4. Number of matrixes representing a configurational isomer of **7**. Depending on the possible symmetry numbers ($\sigma = 2$ or 1), two and four configurational matrixes exist, respectively.

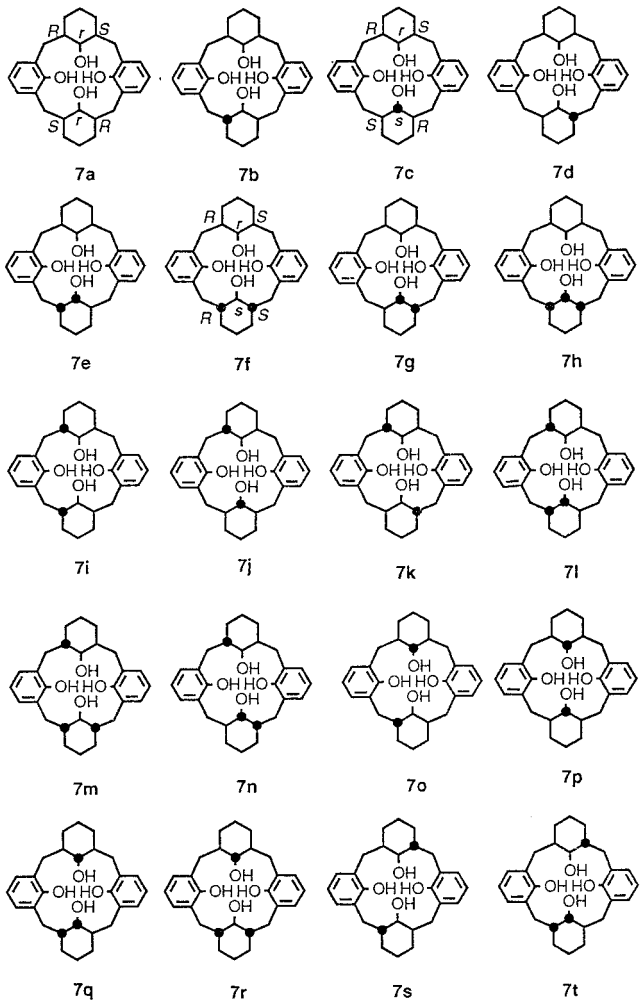


Figure 5. The twenty isomeric forms of **7**.

the case of **7r** the compound adopts the high energy anti-down/gauche-up conformation.

(c) NMR Spectra of 7. The ^{13}C NMR spectrum of the isolated isomer of **7** displays six aromatic signals, eight aliphatic signals in the 25−44 ppm range, and two signals at relatively low field (66.28 and 72.54) which are assigned to the C_α carbons of the two cyclohexanol rings. This is in agreement with a structure of C_s symmetry in which the mirror plane bisects two symmetry nonequivalent cyclohexanol rings. 2D HC correlation spectra and COSY spectra enabled us to assign the ^1H NMR signals at 2.57 and 3.44 to the methine protons at the C_α carbons. The high field signal displays a large coupling constant (^3J = 10.2 Hz) with the protons on the C_β carbons. This is consistent with a diaxial arrangement between the coupled nuclei. The hydroxyl group attached to C_α must be located in the equatorial position. The broad signal at 3.44 corresponds to an equatorial proton, in which the small diequatorial (gauche) coupling is unresolved and therefore its geminal OH group must be axially located. The relative chemical shifts of the axial and equatorial C_α protons are in agreement with previous work on cyclohexyl rings, which indicate that equatorial protons resonate at a lower field than do axial protons.[17] Assuming that both rings are connected to the macrocycle through their equatorial positions, it can be concluded that the configuration of the two rings differs, and whereas one ring possesses *RrS* configuration, the second ring possesses *RsS* configuration (i.e., **7c** or **7f**).

The two low field signals at 2.78 and 3.30 ppm were assigned to the axial protons on the bridging methylene groups.[18] Both signals display a large geminal coupling (14.0 Hz) with their corresponding equatorial protons, but they differ in the size of their vicinal coupling constant with the proton at C_β (^3J = 11.2 and 4.8 Hz). This indicates that whereas one cyclohexyl ring is oriented anti, the other ring is oriented gauche. COSY spectra indicated that the *RrS* ring is oriented anti and the *RsS* ring adopts a gauche conformation. Although both in **7c** and **7f** the *RrS* and *RsS* rings can adopt anti and gauche conformations, respectively (anti-up/gauche-up or anti-down/gauche-down for **7f**, or anti-down/gauche-up or anti-up/gauche-down for **7c**), the NMR data fit better for structure **7f** with anti-down/gauche-down arrangements of the rings.

(d) X-ray Crystallography. A single crystal of **7f** was grown from chloroform/ethanol. The X-ray structure (Figure 2) corroborates that the compound isolated is the *RrS*/*SsR* isomer with the rings oriented in anti-down/gauche-down arrangements, respectively. The H−C_β−C(bridging CH_2)−H(axial) torsional angles of the cyclohexanols are 179° (for the *RrS* ring) and 58° (for the *RsS* ring), i.e., near their ideal staggered values. The OH groups are located in the axial and equatorial positions. As observed for the monocyclohexanol derivatives,[7b] the four hydroxyls are engaged in a circular array of hydrogen bonds

(17) Günther, H. *NMR Spectroscopy*; Wiley: Chichester, 1980; p 72.

(18) In endocalixarenes the axial protons of the bridging methylenes resonate at a lower field than the equatorial protons (Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335). However, in exocalixarenes this behavior is reverted. See: Biali, S. E.; Böhmer, V.; Brenn, J.; Frings, M.; Thondorf, I.; Vogt, W.; Wöhnert, J. *J. Org. Chem.* **1997**, *104*, 5163.

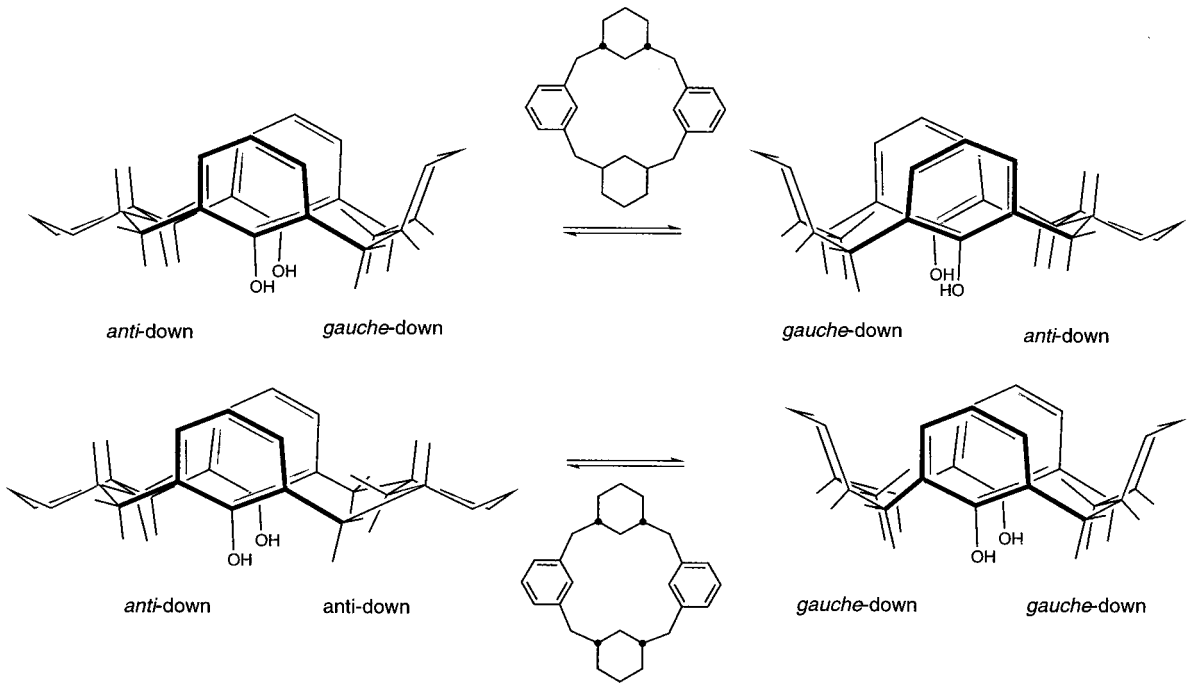
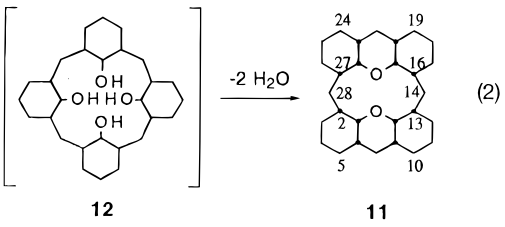


Figure 6. Expected low-energy conformations for the saturated calixarene analogues **10a** (bottom) and **10b** (top).

(O2(ax)···O1: 2.82 Å, O1···O4(eq): 2.72 Å, O4···O3: 2.81 Å, O3···O2: 2.72 Å). The crystallographic conformation is practically identical to that predicted by the MM3 calculations.

On the basis of the MM3 calculations, it can be concluded that the compound isolated (**7f**) does not correspond to the lowest energy product, because the most stable isomer is **7a**. The formation of **7f** can be rationalized if **6a** is an intermediate in the hydrogenation, and attack of the hydrogen in the preferred conformation occurs on the external face of the phenol ring distal to the cyclohexanol.

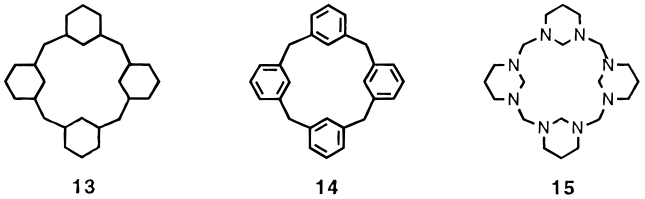
Full Hydrogenation. Hydrogenation of **3** at 120 °C yielded a mixture of products from which one compound was isolated by thin layer chromatography (TLC). This compound displayed in the ^{13}C NMR spectrum with seven signals in the 27.06−44.82 region, and a signal at 79.80 which can be ascribed to a C−O unit. The ^{1}H NMR spectrum displays a signal at 3.66 integrating for four protons which, by analogy with the spectrum of **7f**, can be assigned to the equatorial protons at C_α. Consequently, the four C−O bonds must be located at axial positions.



(2)

X-ray diffraction of the product (Figure 2) indicates that **11** is a saturated diether in which all C−O bonds are located in axial positions. The two perhydroxanthene subunits exist in a cis-syn-cis fusion, and the C−O stereocenters are oriented in an *RSRS* disposition along the macrocycle. To alleviate the steric interactions between the two perhydroxanthene units, the C−C−C bond angles of the bridging methylenes are larger than the tetrahedral value (118.8° and 119.6°).[19] The nonbonded distances between the internal hydrogens are 2.14 and 2.16 Å, and the distance between the perhydroxanthene hydrogens C5−H···H−C10 and C19−H···H−C24 is only 2.04−2.05 Å. Diether **11** is probably formed by the intramolecular dehydration of a tetraalcohol **12** (eq 2) in which the hydrogens at all C_β carbons are located on the same face of the macrocyclic ring. According to MM3 calculations, **11** lies 13.5 kcal mol^{-1} above **4**, which indicates that the latter (obtained at higher temperatures) represents the lowest energy isomer.

High-Temperature Hydrogenation. Catalytic hydrogenation of **3** at high temperatures (250 °C) resulted in the formation of pentacyclo-[19,3,1,1,1,^{3,7}1,^{9,13}1,^{15,19}]octacosane **13**. The formation of **13** suggests that, if cyclohexanol rings are formed in the hydrogenation, they undergo dehydration under the reaction conditions.[20] We found also that the macrocycle **13** can be prepared in good yield by exhaustive catalytic hydrogenation (Pd/C, 250 °C, 600 psi H_2) of [1$_4$] metacyclophane **14**.[21]



(a) Possible Configurational Isomers of 13 and Their Symmetries. To calculate the possible number of isomers of **13** and their symmetries the system is viewed as derived from the desymmetrization of metacyclophane **14** of D_{4h} symmetry.

(19) Steric crowding increases the RCR bond angle in disubstituted methanes. For example, according to X-ray crystallography this angle is 129.3° in ditriptycyl methane (Johnson, C. A.; Guenzi, A.; Nachbar, R. B.; Jr.; Blount, J. F.; Wennerström, O.; Mislow, K. *J. Am. Chem. Soc.* **1982**, *104*, 5163).

(20) Hydrogenation of **11** under the reaction conditions used for the hydrogenation of **3** resulted also in the formation of **13**. This reaction involves not only reductive cleavage of the C−O bonds, but also $R \rightleftarrows S$ isomerization of the C_β carbons.

(21) McMurry, J. E.; Phelan, J. C. *Tetrahedron Lett.* **1991**, *32*, 5655.

Table 2. The 43 Configurational Isomers of **13** and Their Respective Symmetries[a]

symmetry	isomer(s)
D_4	(1010 1010)/(0101 0101)
C_{4v}	(0000 0000)
D_{2d}	(1001 1001), (1100 1100)
C_{2h}	(1111 0000), (1110 0001), (1101 0010), (1010 0101)
C_s	(1100 0000), (1001 0000), (1000 0100), (1000 0001)
C_2	(1000 1000)/(0100 0100),(1110 1000)/(1100 0101),(1110 0010)/(1101 0001), (1101 0100)/(1100 1010), (1010 0110)/(1001 0101)
C_1	(1000 0000)/(0100 0000), (1010 0000)/(0101 0000), (1110 0000)/(1100 0001), (1101 0000)/(1100 0010), (1100 1000)/(1100 0100), (1010 1000)/(0101 0100), (1010 0100)/(1001 0100), (1010 0001)/(1000 0101), (1001 1000)/(1001 0001), (1110 0100)/(1100 1001)

[a] A slash (/) indicates an enantiomeric pair. Symmetries refer to idealized structures.

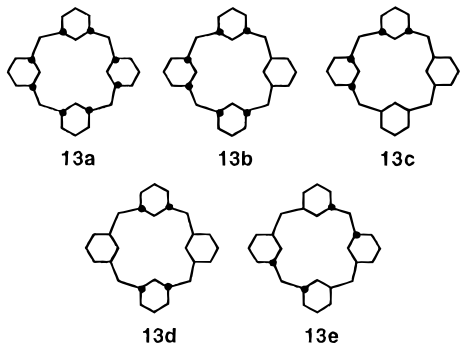
The possible symmetries of the configurational isomers of **13** must correspond to D_{4h} or one of its subgroups (D_4, D_{2d}, C_{4v}, C_4, S_4, C_{2h}, C_2, C_s, C_i, C_1).[22,23] However, not all of these symmetries are possible for the isomers of **13**, because the presence of either a single S_4, C_4, or $S_2(i)$ symmetry operation necessarily requires the presence of additional nontrivial symmetry elements.[24] Moreover, because the presence of the stereocenters is not compatible with a symmetry plane passing through the *xy* plane (cf. Figure 3), no isomer of **13** can belong to the D_{4h} point group. In the isomers possessing C_{2h} or C_s symmetry, the symmetry plane necessarily must be perpendicular to the *xy* plane. The possible symmetries of the systems are therefore limited to D_4, D_{2d}, C_{4v}, C_{2h}, C_s, and C_1.

(b) Ideal Isomer Number. A one-dimensional configurational matrix consisting of eight binary digits can be constructed, which describes the configurations of the eight stereocenters according to the convention depicted in Figure 3.[14] There are 2^8 (256) distinct matrixes, and depending on the symmetry number of a given isomer ($\sigma = 8$ (D_4), 4 (D_{2d}, C_{4v}), 2 (C_{2h}), or 1 (C_1)), one, two, four, and eight different matrixes exist for a given isomer, respectively.

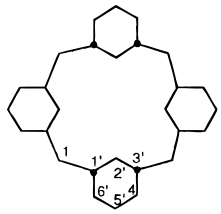
Only two matrixes exist representing isomers of D_4 symmetry ((1010 1010) and (0101 0101)). If the number of symmetry matrixes representing isomers possessing the symmetry of one of the subgroups of D_4 (e.g., C_2) is calculated, necessarily this number will include matrixes possessing the higher (D_4) symmetry. The number of matrixes of a given subgroup is obtained by subtracting from the calculated number of matrixes the number of matrixes representing structures of higher symmetry. As shown in Table 2, there are 43 isomers of the system, which correspond to 11 achiral forms and 16 enantiomeric pairs.

(c) Molecular Mechanics Calculations. From the large number of possible isomers, we restricted ourselves to the potentially low-energy forms, i.e., those in which the methylene groups are attached to the equatorial positions of the cyclohexyl ring (i.e., *RS* configurations of the cyclohexyl rings) (**13a**−**13d**), Scheme 2). MM3 calculations indicate that the structure of lower steric energy is **13d** of D_{2d} symmetry. In the stereoisomer **13a**, the conformation of C_{4v} symmetry represents a transition structure, which can be further minimized to a structure of C_2v symmetry which lies 9.4 kcal mol^{-1} above **13d**. Structure **13e**, in which the methine protons are *trans* and four methylene groups are located at axial positions of the cyclohexyl rings, lies 7.3 kcal mol^{-1} above **13d**.

Scheme 2



Scheme 3



NMR spectra. The saturated metacyclophane **13** displays five signals in the ^{13}C NMR (100.62 MHz, RT), in agreement with a structure in which the four rings as well as pairs of carbons at the 1′/3′ and 4′/6′ positions (cf. Scheme 3) are symmetry equivalent. This indicates that the molecule possesses either D_{2d} or C_{4v} symmetry (e.g., **13a** or **13d**). Notably, the methylene protons at the 2′ position display very different chemical shifts (2′eq: 1.8 ppm, 2′ax: 0.15 ppm). In principle, structures **13a** and **13d** should display different NMR patterns of the bridging methylene protons, because these protons should be homotopic in **13d** and diastereotopic in **13a**. On the basis of the ^{1}H NMR spectrum, structure **13a** cannot be ruled out provided that the bridging methylene protons have similar chemical shifts.

(a) X-ray Crystallography. The molecule crystallized from $CHCl_3$/EtOH with a disordered chloroform molecule. According to the X-ray structure (Figure 2), the configuration of the saturated macrocycle is **13d** (the calculated lowest energy isomer), in which pairs of methine hydrogens at the four rings are arranged alternately above and below the mean macrocyclic plane. Although the molecule possesses crystallographic S_4 symmetry, the deviation from D_{2d} symmetry is small. All rings exist in an anti conformation.

13d is the hydrocarbon analogue of the octaaza macrocycle **15**, the main product of the reaction of 1,3-diaminopropane and formaldehyde.[25] For **15**, the 43 isomeric forms are interconvertible by inversion of the nitrogen atoms. X-ray analysis showed that in its benzene clathrate, **15** adopts a conformation

(22) The symmetries considered correspond to the "averaged symmetries", i.e., the (nonrigid) symmetries which result when all conformational interconversions are fast. The symmetry of the preferred conformation of a given isomer may be identical to or lower than the averaged symmetry.

(23) Donaldson, J. D.; Ross, S. D. *Symmetry and Stereochemistry*; Wiley: New York, 1972.

(24) For example, a C_4 symmetry axis must necessarily coexist with four symmetry planes (C_{4v} point group) or four C_2 axes (D_4 symmetry). The C_2 operation is a trivial symmetry element of the S_4 and C_4 point groups because both $S_4^2 = C_2$ and $C_4^2 = C_2$.

analogous to **13e** in which the bridging methylene groups are alternately disposed in the equatorial and axial positions; in its dichloromethane complex, the conformation adopted is analogous to **13d**.[26,27]

Conclusions

Catalytic hydrogenation (Pd/C) of calixarenes can afford saturated calixarene analogues in which one, two, or all rings have been hydrogenated. The hydroxyl groups seem prone to undergoing dehydration under the reaction conditions.

Experimental Section

Crystallography. Data were measured on an ENRAF-Nonius CAD-4 computer or PW1100/20 Philips Four-Circle Computer-Controlled Diffractometer. Cu Kα (λ = 1.54178 Å) or Mo Kα (λ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. Crystallographic data follow. **7f**: $C_{28}H_{36}O_4$, space group *C*2/*c*, a = 21.138(4) Å, b = 12.151(2) Å, c = 18.737(3) Å, β = 103.42(1)°,V = 4681.2(9) Å^3, z = 8, ρ_{calc} = 1.24 g cm^{-3}, μ(MoKα) = 0.76 cm^{-1}, no. of unique reflections = 4344, no. of reflections with I ≥ 3σ_I = 2423, R = 0.046, R_w = 0.058. **11:** $C_{28}H_{44}O_2$, space group $P2_1$/c, a = 11.248(2) Å, b = 21.303(4) Å, c = 10.654(2) Å, β = 112.70(1)°,V = 2355.1(8) Å^3, z = 4, ρ_{calc} = 1.16 g cm^{-3}, μ(MoKα) = 0.66 cm^{-1}, no. of unique reflections = 3394, no. of reflections with I ≥ 3σ_I = 1930, R = 0.048, R_w = 0.058. **13d**: $C_{28}H_{48}$, space group $P\bar{4}2_1c$, a = 12.065(2) Å, c = 10.068(1) Å, V = 1465.5(5) Å^3, z = 2, ρ_{calc} = 1.14 g cm^{-3}, μ(CuKα) = 29.69 cm^{-1}, no. of unique reflections = 852, no. of reflections with I ≥ 2σ_I = 666, R = 0.096, R_w = 0.132.

Hexahydrocalix[4]arene 6a and Dodecahydrocalixarene 7f. To a solution of 0.30 g calix[4]arene in 60 mL cyclohexane was added 0.5 g Pd/C (10%) and the mixture was hydrogenated (600 psi H_2) at 100 °C for 8 h. After filtration of the catalyst the solvent was evaporated. The desired products were separated by preparative TLC (silica, eluent: CH_2Cl_2, R_f: 0.75 (**6a**) and 0.50 (**7f**)). The compounds were recrystallized from $CHCl_3$/EtOH, yielding **6a** (10%), mp 234−236 °C and **7f** (10%), mp 280−282 °C.

Spectroscopic Data for 6a: ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) 1.20−1.56 (m, 6H), 1.78 (dt, 2H, ^2J = 13.1 Hz, ^3J = 3.0 Hz), 2.39 (dd, 2H, ^2J = 14.2 Hz, ^3J = 3.8 Hz), 2.82 (dd, 2H, ^2J = 14.1 Hz, ^3J = 11.8 Hz), 3.26 (s, 1H), 3.49 (d, 2H, J = 13.8 Hz), 4.22 (d, 2H, ^3J = 13.8 Hz), 6.70 (t, 2H, ^3J = 7.5 Hz), 6.78 (t, 1H, ^3J = 7.5 Hz), 6.84 (dd, 2H, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 6.99 (d, 2H, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.11 (d, 2H, ^3J = 7.5 Hz), 9.91 (br s, 3H, OH). ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 25.62, 28.82, 31.72, 33.72, 43.62, 66.47 (C−O), 121.58, 121.98, 126.70, 127.80, 128.33, 128.51, 128.96, 129.63, 149.42 (C−O), 150.51 (C−O). HRMS calcd for $C_{28}H_{30}O_4$: 430.2144. Found: 430.2164.

Spectroscopic Data for 7f. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 1.11 (dq, 3H, ^2J = 13.7, ^3J = 3.1 Hz), 1.38−1.84 (m, 13H), 2.32 (dd, 2H, ^2J = 14.0, ^3J = 2.8 Hz), 2.38 (dd, 2H, ^2J = 14.0, ^3J = 2.8 Hz), 2.57 (t, 1H, ^3J = 10.2 Hz) 2.78 (dd, 2H, ^2J = 14.0, ^3J = 11.2 Hz), 3.30 (dd, 2H, ^2J = 14.0 Hz, ^3J = 4.8 Hz), 3.44 (s, 1H), 5.00 (s, 1H), 5.91 (s, 1H, OH), 6.70 (t, 2H, ^3J = 7.6 Hz), 6.79 (d, 2H, J = 7.6 Hz), 6.91 (d, 2H, J = 7.6 Hz), 9.52 (s, 2H, OH). ^{13}C NMR (100.62 MHz, $CDCl_3$, rt): δ 25.60, 25.70, 28.56, 30.13, 31.46, 33.90, 43.69, 44.02, 66.28 (C−O), 72.54 (C−O), 119.95, 123.47, 125.86, 129.68, 130.94, 153.37 (C−O). HRMS calcd for $C_{28}H_{36}O_4$: 436.2614. Found: 436.2582.

Diether 11. 0.30 g calix[4]arene dissolved in 60 mL cyclohexane and 0.5 g Pd/C (10%) was hydrogenated (120 °C, 3 h). The residue was separated by preparative TLC (eluent CH_2Cl_2, R_f: 0.9). The compound was purified by recrystallization from $CHCl_3$/EtOH to yield pure **11** (5%), mp 235−238 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 0.60 (d, 2H, ^2J = 18.4 Hz), 1.0−2.0 (m, 36H), 2.64 (m, 2H), 3.66 (s, 4H). ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 27.06, 29.69, 30.70, 33.52, 35.73, 36.15, 44.82, 79.80 (C−O). HRMS calcd for $C_{28}H_{44}O_2$: 412.3341. Found: 412.3351.

Pentacyclo[19,3,1,1^{3,7},1,^{9,13},1^{15,19}]octacosane (13d). To a solution of 0.5 g of calix[4]arene or 0.5 g of [1^4] metacyclophane in 60 mL cyclohexane was added 1.0 g Pd/C (10%). The mixture was hydrogenated for 24 h (250 °C, 600 psi). Recrystallization of the residue (EtOH/$CHCl_3$) afforded 350 mg (65−70%) **13d**, mp 258−260 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 0.14 (dt, 4H, ^2J = 12.5 Hz, ^3J = 11.9 Hz), 0.85 (m, 8H)), 1.04 (m, 8H), 1.25−1.42 (m, 12H), 1.50 (m, 8H), 1.68 (m, 4H), 1.80 (d, 4H, ^2J = 12.5 Hz).^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 26.57, 33.80, 34.46, 35.25, 43.88 ppm. CI MS *m*/*z* 383.5 (M−H).

Acknowledgment. We thank Dr. Shmuel Cohen for the X-ray structure determinations and Prof. Jack M. Harrowfield for preprints of refs 7a and 7b. This research was supported by a grant from the German-Israeli Foundation (GIF) for Scientific Research and Development.

Supporting Information Available: Numbering schemes, tables of atomic coordinates and thermal parameters for **6a**, **7f**, **11**, and **13d** (11 pages). See any current masthead page for ordering and Web access instructions.

JA974097+

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(27) Dale, J.; Romming, C.; Sigvartsen, T. *Acta Chem. Scand.* **1991**, *45*, 1071.