

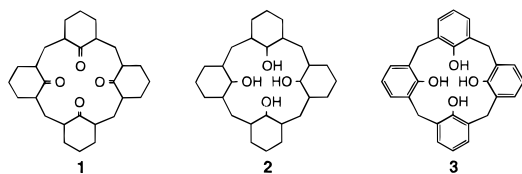
Fully Hydrogenated Calixarene Derivatives: Calix[4]cyclohexanone and Calix[4]cyclohexanol

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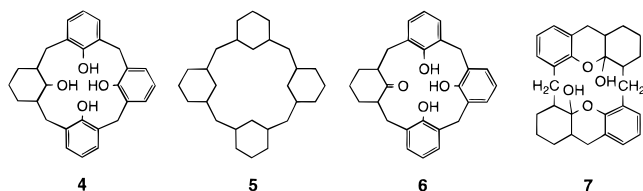
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Saturated [1_n]-metacyclophane derivatives incorporating in the macrocycle cyclohexanone or cyclohexanol rings (e.g., **1** and **2**) are the hitherto unknown hydrogenated analogues of calix[4]arene (**3**).^{1,2} These systems are of interest both as host molecules and as potential synthetic intermediates for the preparation of modified calixarenes (e.g., via reaction at the carbonyl groups of **1** followed by aromatization) and novel host molecules. The stereoselective preparation of **1** and **2** is a challenging task since several stereocenters are present (eight and twelve, respectively) and a large number of configurational isomers are possible.



Hydrogenation of **3** with Pd/C as catalyst (100 °C) yields partially hydrogenated calixarenes containing both phenol and cyclohexanol rings (e.g., **4**) while **5** is obtained at 250 °C.^{3,4} Harrowfield and co-workers⁵ reported that hydrogenation of **3** with RhCl₃·3H₂O/Aliquat 336⁶ (6 atm H₂, rt, 1 week) affords the calixketone **6** (main product) together with the bis-hemiketal **7**.^{5a}



Hydrogenation of **3** with RhCl₃·3H₂O/Aliquat 336/H₂O/CH₂-Cl₂ (200 psi H₂, 90 °C, 2 × 24 h) afforded in 90% yield a mixture of calix[4]cyclohexanone isomers, as suggested by the ¹³C NMR spectrum that displayed several carbonyl signals. Treatment of the mixture with NaOEt/HOEt resulted in epimerization of the stereocenters (Scheme 1). As judged by TLC and by ¹H and ¹³C NMR spectroscopy of the crude product, a single stereoisomer of high symmetry was obtained. The product was purified by

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(1) 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. *Aldrichim. Acta* **1995**, *28*, 1.

(2) For recent studies of cyclophanes incorporating a cyclohexyl ring see: Yang, F.-M.; Lin, S.-T. *J. Org. Chem.* **1997**, *62*, 2727. Ernst, L.; Hopf, H.; Savinsky, R. *Liebigh Ann./Rec.* **1997**, 1915.

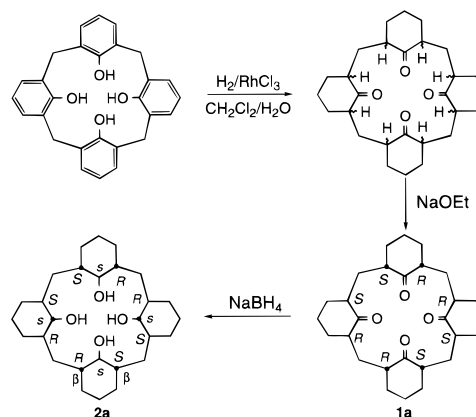
(3) Columbus, I.; Biali, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 3060.

(4) Hydrogenation of **3** with Raney Ni under drastic conditions (1450 psi H₂, Raney Ni/*i*-PrOH/240 °C) afforded a saturated diether (Grynszpan, F.; Biali, S. E. *Chem. Commun.* **1996**, 195).

(5) (a) Bilyk, A.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *Am. Chem. Soc. Div. Polym. Chem. Prepr.* **1997**, *38*, 222. (b) Bilyk, A.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1997**, 4251.

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

Scheme 1



recrystallization from CHCl₃/EtOH affording pure calix[4]cyclohexanone in 40% yield.⁷ This compound most likely corresponds to the lowest energy form, and since no other stereoisomer could be detected by NMR, the energy gap to its closest energy isomer must be relatively large.

Calix[4]cyclohexanone **1a** crystallized with a CHCl₃ molecule that was partially lost during the accumulation of diffraction data.⁸ As indicated by X-ray crystallography, the configuration of the stereocenters is *RS SR RS SR* (**1a**, cf. Scheme 1)⁹ with the molecule possessing crystallographic *S*₄ symmetry, but the deviation from *D*_{2d} symmetry is small.^{8,9} The cyclohexanones are connected to the macrocycle through their equatorial positions, and pairs of methine hydrogens on the rings are alternately oriented above and below the mean macrocyclic plane (Figure 1). The carbonyl groups on neighboring rings are oriented in antiparallel orientations. MM3 calculations¹⁰ indicate that a cone-like conformation with all carbonyls nearly parallel lies 18.8 kcal mol⁻¹ above the crystal conformation. Part of this energy gap is due to the dipole–dipole repulsions present when the carbonyls are oriented in parallel.

Treatment of calix[4]cyclohexanone **1a** with NaBH₄ afforded a single product (Scheme 1) in 30% yield after recrystallization from CHCl₃/EtOH. The compound displayed in the ¹³C NMR (100.62 MHz, CDCl₃, RT) nine signals in agreement with a structure of *C*_{2v} symmetry.⁷ Two *CHOH* triplets were observed in the ¹H NMR spectrum at 2.88 and 3.37 ppm, which on the basis of their coupling constant (³*J* = 9.6 and 10.1 Hz, values indicate an anti relationship to the vicinal methine protons) were ascribed to axial protons. The OH groups are therefore located at equatorial positions of the macrocycle, and assuming that the stereocenters of the starting material **1a** were not affected by the NaBH₄ reduction, it can be concluded that the configuration of the product obtained is *RsS SsR RsS SsR* (**2a**). Two OH signals were observed in the ¹H NMR (CDCl₃) at δ 5.51 and 6.08 ppm, their relative downfield shifts suggesting the involvement of the OH protons in hydrogen bonds. X-ray diffraction of a single

(7) ¹³C NMR data: (100.62 MHz, CDCl₃, rt) **1a**, δ 25.44, 30.15, 38.52, 49.41, 216.85 (C=O) ppm; **2a**, δ 25.61, 26.76, 29.70, 32.77, 35.33, 40.52, 42.58, 69.19 (C–O), 80.04 (C–O) ppm.

(8) Crystallographic data: **1a**, C₂₈H₄₀O₄·0.88CHCl₃, space group *P*4̄₂*c*, *a* = 11.917(3) Å, *c* = 10.305(3) Å, *V* = 1463.5(6) Å³, *z* = 2, ρ_{calc} = 1.24 g cm⁻³, μ(Cu Kα) = 28.15 cm⁻¹, no. of unique reflections = 871, no. of reflections with *I* ≥ 3σ_{*I*} is 652, *R* = 0.074, *R*_w = 0.111; **2a**, C₂₈H₄₈O₄, space group *P*2₁/*n*, *a* = 20.971(5) Å, *b* = 11.261(2) Å, *c* = 11.480(2) Å, β = 104.33-(2)°, *V* = 2626.7(9) Å³, *z* = 4, ρ_{calc} = 1.14 g cm⁻³, μ(Mo Kα) = 0.69 cm⁻¹, no. of unique reflections = 3888, no. of reflections with *I* ≥ 2σ_{*I*} is 2660, *R* = 0.094, *R*_w = 0.110.

(9) A similar disposition of stereocenters was found for the lowest energy isomer of the saturated metacyclophane **5** (ref 3).

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

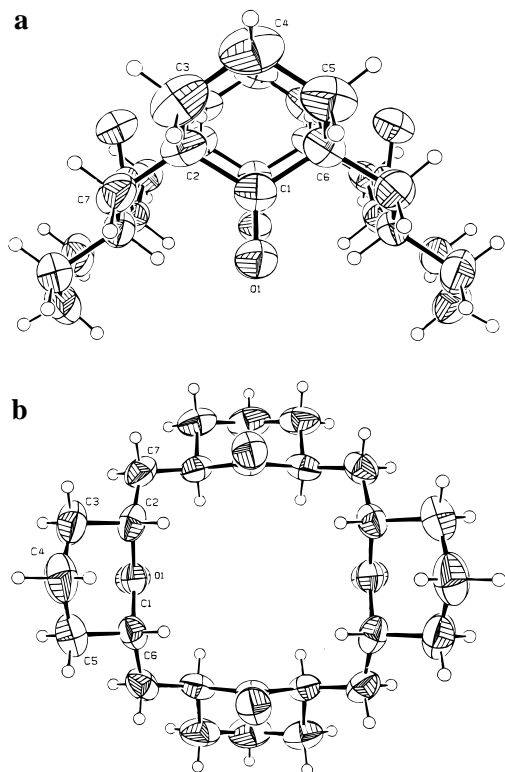


Figure 1. Side (a) and top (b) view of the molecular structure of the calix[4]cyclohexanone **1a**.

crystal of **2a** grown from $\text{CHCl}_3/\text{EtOH}$ corroborated this assignment (Figure 2).^{8,11} The molecule exists in a cone-like conformation in which two distal rings are orienting the methine hydrogens at C_β “in” (toward the cavity center) and two are orienting them “out”. Although the hydroxyl protons could not be located, the nonbonded $\text{O}\cdots\text{O}$ distances ($\text{O1}\cdots\text{O2}$, $\text{O3}\cdots\text{O4}$, 2.71 Å; $\text{O2}\cdots\text{O3}$, $\text{O1}\cdots\text{O4}$, 2.72 Å) suggest that the four equatorial OH groups are engaged in a circular array of hydrogen bonds.

The rotational barrier of **2a** was determined by using the saturation transfer technique that is particularly suitable for the determination of high rotational barriers.¹³ The rotational process is ascribed to a cone-to-cone inversion, which exchanges between the cyclohexyl rings with “in” and “out” methine protons at C_β (Figure 3). The barrier of **2a** ($\Delta G^\ddagger = 22.1 \text{ kcal mol}^{-1}$ at 389 K) is 6.4 kcal mol^{-1} higher than the cone-to-cone barrier of the parent **3**,¹⁴ suggesting that the rotation through the annulus of a cyclohexanol ring in **2a** is energetically more demanding than the rotation of a phenol group in the parent **3**. Work is in progress to exploit the synthetic availability of **1a** and **2a** for the preparation of modified calixarenes.

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(11) The stereoselectivity observed in the NaBH_4 reduction of the carbonyl groups of **1a** is similar to that reported for **6** (ref 5b) since in both cases the hydride attacks preferentially the carbonyl face anti to the methine hydrogens.

(12) Interestingly, according to MM3 calculations, the *RrS SrR RrS SrR* isomer with axial dispositions of the OH groups and no intramolecular hydrogen bonds is 1 kcal mol^{-1} lower in energy than **2a**. This suggests that repulsive steric interactions are present as a result of the equatorial dispositions of the hydroxyls of **2a**. A similar behavior was observed for **4** (ref 3) where MM3 calculations indicate that the *RrS* configuration of the cyclohexanol ring (with axial disposition of the OH when the cyclohexanol is attached through its equatorial positions) is of lower energy than the *RsS* form.

(13) Dahlquist, F. W.; Longmuir, K. J.; Du Vernet, R. B. *J. Magn. Reson.* **1975**, *17*, 406. The experiment was conducted by selectively exciting (180° pulse) the triplet signal at 2.88 ppm (at 389 K) and recording the spectra after increasingly longer delay times.

(14) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

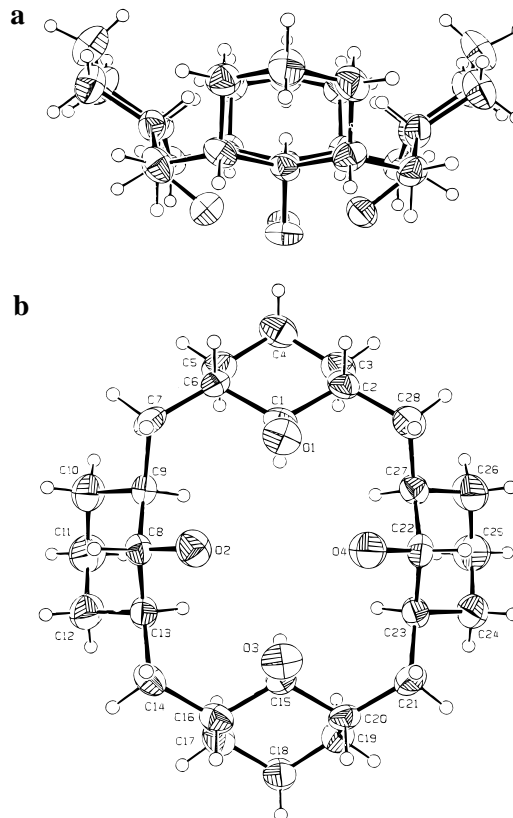


Figure 2. Side (a) and top (b) view of the X-ray structure of the calix[4]cyclohexanol **2a**.

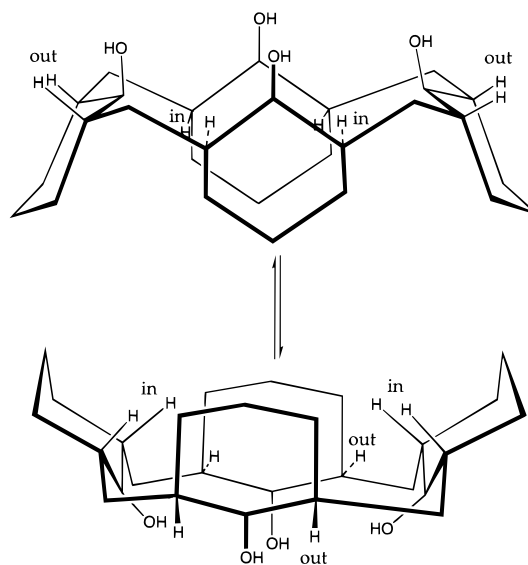


Figure 3. Cone-to-cone ring inversion in calix[4]cyclohexanol **2a**. For clarity, only the methine protons at C_β are shown. The rotational process involves rotations of the cyclohexanol rings through the annulus of the macrocycle, and results in the mutual exchange of the two types of rings (with methine protons at C_β pointing “out” or “in”).

NMR determinations. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supporting Information Available: Tables of atomic and thermal parameters for **1a** and **2a** (7 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.