Face Selectivity in the Hydrogenation of Calixarene Ethers

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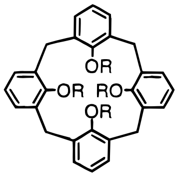
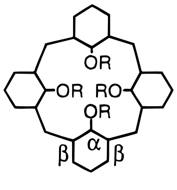
Exhaustive hydrogenation of calix[4]arene derivatives (e.g., **1**) formally affords saturated [1$_4$]metacyclophanes **2** with great stereochemical complexity.[1−3] These saturated systems can provide unique insights to the conformational restrictions imposed on cyclohexane rings incorporated in a macrocycle. Control of such conformations is a key element for the design of shape-selective host molecules based on saturated building blocks. In this paper, we show that the hydrogenation of conformationally fixed calix[4]arenes proceeds with high diastereoselectivity and produces saturated systems with unusual conformations of the cyclohexane rings.



1 R = Pr



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The calix[4]arene propyl ether **1** can be prepared stereospecifically in atropisomeric forms (cone, partial cone (*paco*), 1,3-alternate (*1,3-alt*), and 1,2-alternate (*1,2-alt*)).[4] These forms do not interconvert on the laboratory time scale, even at high temperatures, because the propyl groups hinder the rotation of the rings through the macrocyclic annulus.

In the atropisomers of **1** the two faces of each ring are diastereotopic. For example, the faces of any of the rings of **1**-*cone* are symmetry unequivalent; one is directed inside the cavity ("*endo*" face) and the other outside ("*exo*" face, Figure 1). All-syn attack of the hydrogen atoms on the endo or exo face of a given ring will result in a saturated ring with an all-syn-endo or all-syn-exo disposition of the methine protons at C_α and C_β, respectively.[5] Interconversion between these two forms requires rotation through the annulus of the saturated ring, but by analogy to **1**, in the saturated derivatives the process is expected to be precluded by the bulky propoxy groups. On the basis of steric considerations it can be expected that hydrogenation of **1** should take place by attack of the less hindered exo face.[6] All-exo attack of **1**-*cone*, **1**-*paco*, and **1**-*1,3-alt* should afford products (**3a**−**c**, respectively) differing in the pattern of stereocenters (Figure 1).

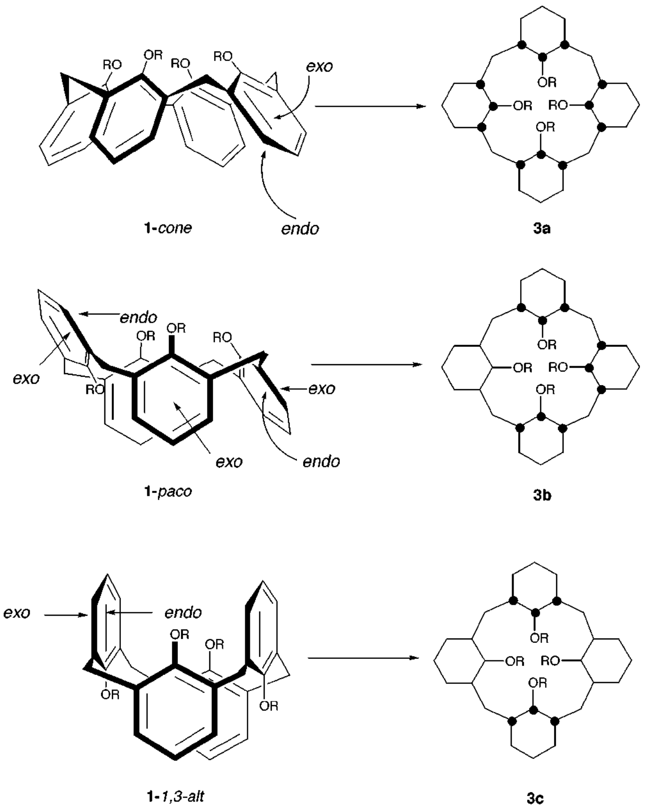

Figure 1. Exo and endo faces and schematic representation of the configurations of the products obtained from the all-exo or all-endo hydrogenation of **1**-*cone* (i), **1**-*paco* (ii), and **1**-*1,3-alt* (iii). The dots represent hydrogens pointing toward the observer.

Separate hydrogenation experiments on **1**-*cone*, **1**-*paco*, and **1**-*1,3-alt* (Pd/C, 600 psi H_2, C_6H_{12}, 120 °C) afforded stereospecifically **3a**-*cone*, **3b**-*paco*, and **3c**-*1,3-alt*, respectively, indicating that no rotation through the annulus occurred under the reaction conditions.[7] The ^{1}H NMR spectra of the three products display a small vicinal coupling constant between the protons at C_α and C_β ($^3J = 4.8{-}5.0$ Hz) suggesting syn-periplanar arrangements, i.e., cis relationships between the three protons. The three hydrogens

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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.

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(3) For studies on the hydrogenation of calixarenes, see: (a) Grynszpan, F.; Biali, S. E. *Chem. Commun.* **1996**, 195. (b) Bilyk, A.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *An. Quim. Int. Ed.* **1997**, *93*, 363. (c) Bilyk, A.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1997**, 4251. (d) Columbus, I.; Biali, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 3060. (e) Columbus, I.; Haj-Zaroubi, M.; Biali, S. E. *J. Am. Chem. Soc.* in press.

(4) (a) Verboom, W.; Datta, S.; Asfari, Z.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 5394. (b) Ikeda, A.; Nagasaki, T.; Araki, K.; Shinkai, S. *Tetrahedron* **1992**, *48*, 1059. (c) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991,** *56*, 4955. (d) Iki, H.; Kikuchi, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 205.

(5) Hydrogenation of triptycene under kinetic control occurs in an all-syn fashion. See: Farina, M.; Morandi, C.; Mantica, E.; Botta, D. *J. Org. Chem.* **1977**, *42*, 2399.

(6) $Cr(CO)_3$ complexation of **1** occurs on the exo face. See: Iki, H.; Kikuchi, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 205.

(7) To 100 mg of **1**-*cone*, **1**-*partial cone*, or **1**-*1,3-alt* dissolved in 50 mL cyclohexane were added 200 mg of Pd/C. Hydrogenation in a Parr reactor (600 psi H_2, 120 °C, 16 h) followed by crystallization from $CHCl_3$/EtOH afforded pure products in ca. 50% yield each. **3a**-*cone:* mp 240−242 °C; ^{13}C NMR (100.62 MHz, $CDCl_3$, rt) δ 10.78, 16.18, 22.25, 23.28, 30.25, 41.71, 68.88, 82.43 ppm. **3b**-*partial cone:* mp 185−188 °C; ^{13}C NMR δ 10.74, 10.93, 11.22, 15.23, 15.55, 16.36, 21.58, 23.33, 23.51, 23.80, 24.19, 28.19, 28.51, 29.37, 30.81, 36.99, 37.03, 41.03, 41.86, 68.59, 68.78, 68.92, 80.98, 81.96, 82.29 ppm. **3c**-*1,3-alt*: mp 228−230 °C; ^{13}C NMR δ 11.11, 15.22, 23.41, 23.73, 28.23, 36.77, 68.72, 80.99 ppm.

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at C_α and C_β are therefore delivered to the same face. Because **3a**-*cone* and **3c**-*1,3-alt* display eight signals in the ^{13}C NMR spectrum it can be concluded that the same face of the four symmetry-equivalent rings was attacked.[7] The chemical shifts of the C_α protons are in the 3.13−3.23 ppm range and are consistent with axial *H*COR protons.[3d] Observation that in each ring the C_α proton is syn-periplanar to the protons at C_β and that the latter must be located at equatorial positions indicates that the cyclohexane rings are connected to the macrocycle through their axial positions.[8]

The all-axial connection of the cyclohexane rings to the macrocycle in **3a**-*cone*, **3b**-*paco*, and **3c**-*1,3-alt* is rather surprising since a priori it could be naively expected that the low-energy forms will be those in which the cyclohexane groups are connected through their equatorial positions.[9,10] In principle, the forms obtained experimentally (axial-exo) could convert, by chair inversion of the four cyclohexane rings, into structures with all cyclohexanes connected through their equatorial positions and with the OPr located in axial positions (equatorial-exo forms). This process does not involve rotation through the annulus; therefore, the endo-exo and the up−down stereochemistries of each isomer would be retained.

MM3 calculations performed on **3a**−**c** indicate that the experimentally obtained axial-exo form is 6.9−14.8 kcal mol^{-1} higher in energy than the lowest energy equatorial-endo form in which the methine protons point inside the annulus (Figure 2) but several kcal mol^{-1} lower than the equatorial-exo that would result from simple cyclohexane ring inversion.[11,12] The isolation of the axial-exo form of **3c** indicates that the barrier for the ring inversion of the rings and/or rotation through the annulus is substantial.[13] Heating a sample of **3c**-*1,3-alt* in a sealed glass tube to 573 K for 24 h did not result in any appreciable change.[14] From the lower limit of the $t_{1/2}$ of the axial-exo $\rightleftarrows$ equatorial-endo isomerization at 573K (>1 day), a lower limit for the inversion/rotation through the annulus barrier of 47.6 kcal mol^{-1} is obtained.

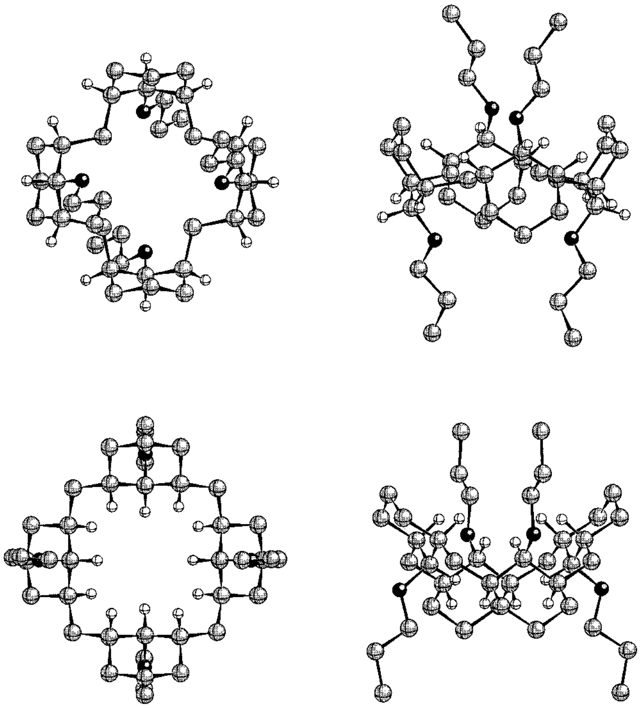

Figure 2. Top and side view of the calculated (MM3) geometries of the axial-exo (top) and equatorial-endo (bottom) forms of **3c**-*1,3-alt*. All hydrogens, except those at C_α and C_β, were omitted for clarity.

Examination of the calculated (MM3) geometries of the axial and equatorial forms of **3c**-*1,3-alt* allows one to rationalize why the high energy "axial" form is obtained preferentially. In the equatorial-endo form the methine hydrogens at C_α and C_β are pointing into the cavity (Figure 2), in contrast to the "axial-exo" form that has these hydrogens oriented in the opposite direction. The formation of the lower energy equatorial form would require that all hydrogens be delivered to the endo face of **1**-*1,3-alt*; however, this face cannot be approached by the catalyst and only exo attack occurs.[15] Because rotation through the annulus (a process that interconverts between endo and exo faces) is precluded by the bulky propyl groups, the high energy axial-exo form is obtained exclusively.

In summary, hydrogenation of the atropisomers of **1** occurs in an exo, all-syn fashion. Judicious selection of the atropisomeric starting material allows control of the pattern of stereocenters in the hydrogenated product. Notably, the high energy axial-exo isomers are formed that are conformationally stable due to the high barrier to inversion/rotation through the annulus.

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[8] The X-ray structures of **3c**-*1,3-alt* and **3b**-*paco* could not be satisfactorily refined due to the disorder of the propyl groups. Although of poor quality, the crystallographic data corroborate the stereochemical assignment, namely hydrogens at C_α and C_β located at the exo face in a cis relationship and axial connections of the cyclohexanes to the macrocycle.

[9] For recent reviews on the conformation of cyclohexane rings, see: (a) *Conformational Behavior of Six Membered Rings*; Juaristi, E., Ed.; VCH: 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.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

[10] The equatorial disposition of alkyl group in a cyclohexane is favored over the axial one. For exceptions to this rule, 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.

[11] Allinger, N. L. *Molecular Mechanics. Operating Instructions for the MM3 Program. 1989 Force Field (updated 5/6/92),* Technical Utilization Corp.

[12] According to X-ray diffraction, the lowest energy form of a tetraketone analogue of **2** possess a pattern of stereocenters at C_β identical to **3c**-*1,3-alt* and adopts the equatorial-endo conformation (ref 3e).

[13] The highest barrier for ring inversion of a cyclohexane ring determined experimentally so far ($\Delta G^\ddagger = 37.5$ kcal mol^{-1}) has been reported for a crowded rotane. See: Fitjer, L.; Steeneck, C.; Gaini-Rahimi, S.; Schröder, U.; Justus, K.; Puder, P.; Dittmer, M.; Hassler, C.; Weiser, J.; Noltemeyer, M.; Teichert, M. *J. Am. Chem. Soc.* **1998**, *120*, 317.

[14] Heating **3c**-*1,3-alt* at a higher temperature (650 K) for 5 days resulted only in partial decomposition of the sample, as indicated by the ^{1}H NMR spectrum, which showed the presence of starting material and propanol.

[15] Inspection of models and MM3 calculations indicate that equatorial-exo arrangement of the cyclohexanes in **3a**-*cone*, **3b**-*partial cone*, and **3c**-*1,3-alt* results in severely strained structures.