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Oxygenation of Calixarene Phenol Rings

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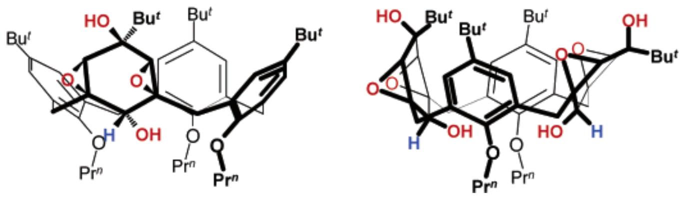
ABSTRACT



The first examples of epoxy-*p*-quinol and diepoxy-*p*-quinol calixarene derivatives have been obtained by base-promoted direct addition of O_2 (oxygenation) to calixarene phenol rings. The regio- and stereochemistry of these derivatives was determined by 2D NMR studies, in conjunction with MM3 calculations, and X-ray crystallography. Both the oxygenation and the subsequent carbonyl reduction occur with a preferential attack to the less hindered *exo* face of the calixarene rings.

In the past two decades, considerable attention has been devoted to the chemical modification of calixarenes, which has been used to profoundly alter the chemical and supramolecular properties of the parent macrocycles.[1] The more common transformations are usually performed by functionalization at the *para* positions of the aromatic rings (the *upper rim*) or at the phenolic hydroxyls (the *lower rim*).[1] Largely less investigated has been the modification of the aromatic "walls" of the calix cavity,[2] which include their hydrogenation to cyclohexane-based derivatives[3] or their oxidation to quinone[4] or dienone[5] compounds.

In this regard, it can be envisaged that the introduction of oxygenated functions into the calix walls would give rise to polar derivatives[6] with novel and interesting supramolecular properties. One way to introduce these functions in a 2,4,6-trisubstituted phenol ring is the direct addition of molecular oxygen (oxygenation) to the corresponding phenoxide anion to give epoxy-*o*-quinol or epoxy-*p*-quinol derivatives,[7] which are amenable of further synthetic elaboration. This observation prompted us to investigate the oxygenation of calixarene phenol rings and we wish to report here the first examples of epoxy-*p*-quinol and diepoxy-*p*-quinol calixarene derivatives.[8]

As a case study to define the regio- and stereoselectivity of the reaction, we first studied the direct oxygenation of

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(1) For general reviews on calixarenes, see: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713. (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J., Eds.; Kluwer: Dordrecht, 2001.

(2) For a review on the oxidation and reduction of calixarene aromatic rings, see: Biali, S. E. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J., Eds.; Kluwer: Dordrecht, 2001; Chapter 14, pp 266−279.

(3) (a) Columbus, I.; Haj-Zaroubi, M.; Biali, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 11806 and references therein. (b) Bilyk, A.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1997**, 4251 and references therein.

(4) (a) Webber, P. R. A.; Beer, P. D.; Chen, G. Z.; Felix, V.; Drew, M. G. B. *J. Am. Chem. Soc.* **2003**, *125*, 5774. (b) Gaeta, C.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 9155.

(5) (a) Biali, S. E. *Synlett* **2003**, 1. (b) Gaeta, C.; Gregoli, L.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2002**, *43*, 8875. (c) Consoli, G. M. L.; Geraci, C.; Cunsolo, F.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 53.

(6) Polar, nonionic calixarene derivatives have also been obtained by appending hydrophilic groups: (a) Grote Gansey, M. H. B.; Steemers, F. J.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1997**, 643. (b) Segura, M.; Sansone, F.; Casnati, A.; Ungaro, R. *Synthesis* **2001**, 2105 and references therein.

(7) (a) Nishinaga, A.; Itahara, T.; Shimizu, T.; Matsuura, T. *J. Am. Chem. Soc.* **1978**, *100*, 1820. (b) Nishinaga, A.; Itahara, T.; Matsuura, T.; Rieker, A.; Koch, D.; Albert, K.; Hitchcock, P. B. *J. Am. Chem. Soc.* **1978**, *100*, 1826. (c) Nishinaga, A.; Shimizu, T.; Matsuura, T. *J. Org. Chem.* **1979**, *44*, 2983.

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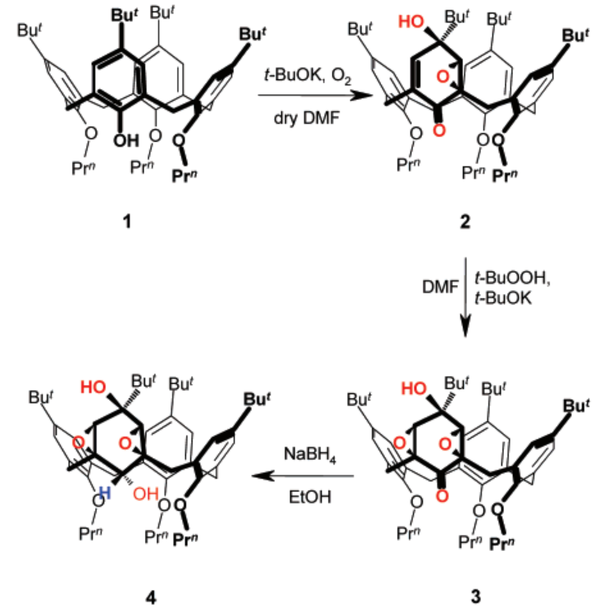
Scheme 1



tripropoxycalix[4]arene **1**,[9] bearing a single phenol ring. Therefore, O_2 was bubbled into a solution of **1** in dry DMF, in the presence of *t*-BuOK, at 15 °C for ca. 5 h, under conditions similar to those reported by Nishinaga *et al*.,[7] to afford epoxy-*p*-quinol calix[4]arene **2** in 20% yield (see the Supporting Information), after column chromatography of the crude reaction mixture (Scheme 1).

The structure of **2** was assigned by spectral analysis. In particular, the presence of a pseudomolecular ion peak at m/z 807 in the ESI(+) mass spectrum confirmed the molecular formula. The asymmetrical structure and the presence of the epoxyquinol moiety were confirmed by the pertinent signals in the ^{1}H and ^{13}C NMR spectra [^{1}H NMR δ 5.90 (s, C═CH, 1H), 3.40 (d, epoxy-H, $J = 2.4$ Hz, 1H), -0.17, 1.09, 1.26, 1.27 (s, *t*-Bu-H, 9H each); ^{13}C NMR δ 187.2 (s, C═O), 60.9 (d, epoxy-CH), 62.5 (s, epoxy-C), 72.5 (s, C-OH)]. However, these data were compatible with both epoxy-*o*- or -*p*-quinol regioisomers. The latter structure was assigned to **2** on the basis of a 2D HMBC NMR spectrum in which was present, *inter alia*, the crucial ^3J correlation at $-0.17/72.5$ ppm between the H-signal of *t*-Bu group of the oxygenated ring and the C-singlet of the tertiary alcohol carbon.

As concerns the stereochemistry of **2**, the *cis* configuration of the hydroxy and epoxy groups can be supposed on the basis of mechanistic considerations,[7a] but the *exo* or *endo* face selectivity of the oxygenation remains to be defined. The unusually shielded signal at -0.17 ppm of the *t*-Bu group of the oxygenated ring is indicative of the self-inclusion of this group inside the calix cavity and suggests an *exo* attack. Both suppositions were confirmed by the presence of the relevant cross-peaks in the NOESY spectrum compared with the MM3 energy-minimized molecular structures[10] of the possible stereoisomers (Figure 1). In particular, strong NOEs were observed between the shielded *t*-Bu signal at -0.17 ppm and those of the two proximal *t*-Bu groups at 1.09 and 1.26 ppm, confirming its *endo*-calix spatial positioning.

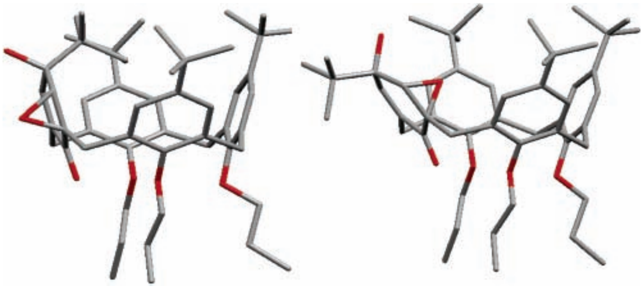


Figure 1. Lowest MM3-energy structures (CHCl$_3$, GB/SA implicit model solvent) of the *exo* (left) and *endo* (right) stereoisomers of epoxy-*p*-quinol calix[4]arene **2**.

The presence of the conjugated enone system in **2** allows the easy introduction of a further oxygenated function by epoxidation with *t*-BuOOH under basic conditions. In this way, epoxy-*p*-quinol **2** was converted to diepoxy-*p*-quinol **3** (45% yield) in the presence of *t*-BuOK, in dry DMF, at room temperature (0.5 h, Scheme 1, see the Supporting Information). Interestingly, workable amounts of **3** (15% yield) were also obtained in the direct oxygenation of **1** at higher temperatures (75 °C).

The structure of **3** was readily assigned on the basis of the presence in its ^{1}H NMR spectrum of a single 2H signal for epoxy-H at 3.33 ppm, which also indicated a C_s symmetry (confirmed by the presence of three 1:2:1 *t*-Bu singlets). Obviously, this symmetry is only compatible with two *cis* epoxy rings, only obtainable with an *exo* attack of the peroxide.

The ketone function of **3** was easily reduced to the corresponding alcohol by treatment with NaBH$_4$ in EtOH to give diepoxy-diol **4** in quantitative yield (Scheme 1, see the Supporting Information). The observation of NOESY correlations between the carbinolic CH and both the adjacent equatorial and axial ArCH$_2$ protons (see the Supporting Information) demonstrated that the hydride attack was again *exo*, giving a *trans* configuration of the secondary OH with respect to the diepoxy and tertiary OH groups.

The above results induced us to extend the oxygenation reaction to *syn*-distal dipropoxycalix[4]arene **5**,[11] which under more forcing conditions (50 °C, 48 h) with respect to **1** gave directly the bis(diepoxy-*p*-quinol) **6** in 28% yield (Scheme 2, see the Supporting Information).

The molecular mass of **6** was confirmed by a pseudomolecular ion at m/z 829 in the ESI(+) MS spectrum, while

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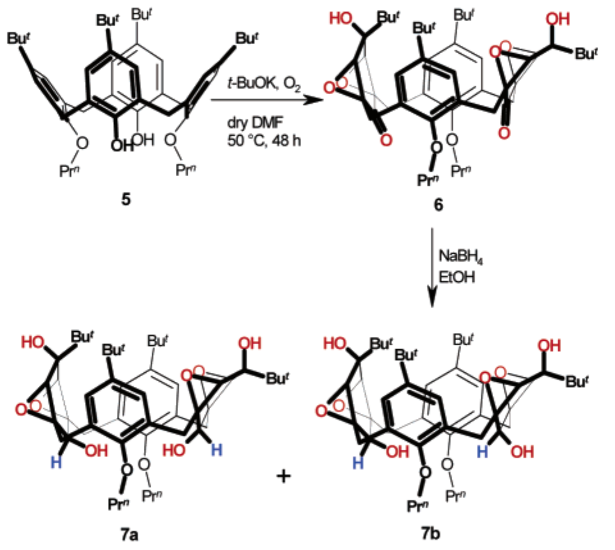
[8] For an example of calixarene bearing epoxy rings, see: Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495.

[9] Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.

[10] Molecular modeling was performed with the MacroModel-7.2/Maestro-4.1 program: Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

[11] Iwamoto, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325.

Scheme 2



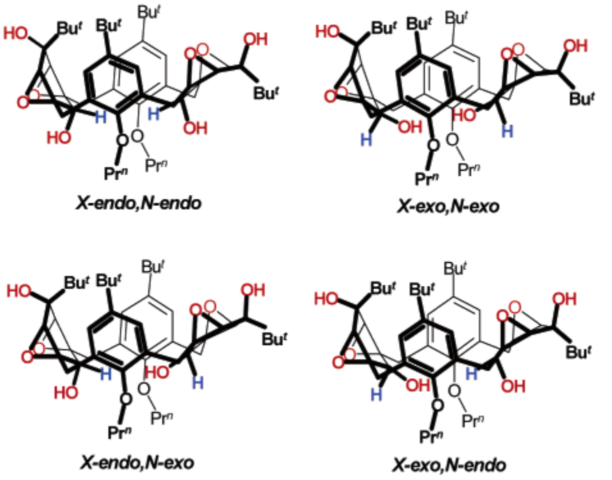


Figure 2. Four possible steroisomers obtainable by $NaBH_4$ reduction of bis(diepoxy-*p*-quinol) **6**.

two distinct 2H epoxy signals at 3.60 and 3.80 ppm and two carbonyl resonances at 193.9 and 195.6 ppm in its ^1H and ^{13}C NMR spectra, respectively, were indicative of two nonequivalent diepoxy-*p*-quinol moieties with a C_s molecular symmetry. As above, this regiochemistry was fully confirmed by means of a 2D HMBC NMR spectrum in which were present two ^3J correlations at 1.17/72.3 and 1.10/72.0 ppm between the H-signals of *t*-Bu groups of oxygenated rings and the pertinent C−OH singlets.

As concerns the stereochemistry, in analogy to the reaction leading to **3**, it can be supposed a *cis* configuration of the two epoxy and the hydroxy groups in each of the oxygenated moieties. The nonequivalence of these rings and the C_s symmetry are then only compatible with an opposite *exo* and *endo* attack of the oxygen on the two phenol rings of **5**. This was confirmed by a NOESY cross-peak at 3.80/6.77 ppm between the *exo*-epoxy-H and the close ArH, which was absent for the *endo*-epoxy-H at 3.60 ppm and the pertinent ArH at 7.09 ppm (see the Supporting Information). This stereochemical outcome could be expected by considering the steric crowding that would be caused by two *exo* attacks to the calix[4]arene in the cone conformation. Then, it is plausible that the second oxygenation step should occur on a partial-cone conformer with the inverted phenol ring.

The treatment of **6** with $NaBH_4$ in EtOH resulted in the formation of two stereoisomeric tetraepoxytetrols **7a** and **7b**, isolated in 35% and 15% yield, respectively, after column chromatography on silica gel (Scheme 2, see the Supporting Information). Clearly, their stereoisomerism should arise from the *exo* or *endo* attack of $NaBH_4$ to the ketone function of the ring bearing either *exo*-epoxides (*X*-ring) or *endo*-epoxides (*N*-ring). Obviously, this should lead, in principle, to four stereoisomers, namely *X-exo*,*N-exo*, *X-endo*,*N-endo*, *X-exo*,*N-endo*, and *X-endo*,*N-exo* (Figure 2).

A detailed 2D NMR study in conjunction with MM3 calculations demonstrated that for **7a** the hydride attack was *exo* to both *X* and *N* rings (*X-exo*,*N-exo*) to give a *trans* and *cis* configuration, respectively, of the secondary OH with respect to the diepoxy groups. In particular, strong cross-peaks were observed at 4.51/3.48 and 4.61/3.57 ppm in the NOESY spectrum of **7a**, between the carbinolic CH signals and the adjacent axial $ArCH_2$ protons, indicating their *syn* relative orientation. Interestingly, both secondary OH signals resonate as doublets, due to their coupling with the pertinent methine, indicating a slow exchange.

In a similar way, strong NOESY cross-peaks at 4.46/3.48 ppm, between the carbinolic CH of *X*-ring and the adjacent axial $ArCH_2$ protons, and at 4.61/3.85 ppm between the OH resonance of *N*-ring and the other axial $ArCH_2$ protons, demonstrated a *X-exo*,*N-endo* attack for **7b**, to give a *trans* configuration of the secondary OH with respect to the diepoxy groups of both *X* and *N* rings.

A definitive proof of the stereochemistry of **7a** was obtained by X-ray analysis of a single crystal grown from CH_2Cl_2/MeOH (Figure 3).[12] In the solid state, calixarene **7a**

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(12) Crystal data for **7a**: $C_{50}H_{72}O_{10}\cdot CH_3OH\cdot H_2O$, $M_r = 883.17$, monoclinic, space group $P21/n$ (No. 14), $a = 16.099(2)$ Å, $b = 18.769(10)$ Å, $c = 16.860(3)$ Å, $\beta = 91.67(1)°$, $V = 5092(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.15$ g cm^{-3}, colorless crystals from CH_2Cl_2/MeOH, crystal dimensions 0.18 × 0.23 × 0.37 mm, $\theta - 2\theta$ scan ($2\theta_{max} = 124.4°$), $F(000) = 1920$, room temperature. Of 8317 measured reflections, 8025 were independent ($R_{int} = 0.022$). Data were collected with a Rigaku AFC5R diffractometer with graphite-monochromated Cu Kα radiation and a 12 kW rotating anode generator. The data were corrected for Lorentz and polarization effects, but no correction was applied for absorption [$\mu(Cu_{k\alpha}) = 6.60$ cm^{-1}] or decay. The structure was solved (direct methods) and refined with the program SIR 97.[13] Non-hydrogen atoms were refined anisotropically except for one solvent molecule (MeOH) refined isotropically because of disorder. All hydrogen atoms (apart from OH) were positioned geometrically (riding model). Final refinements were carried out according to the full-matrix least-squares method based on 4627 observed reflections with $F_o > 8\sigma(F_o)$ and 558 variable parameters (8.3 refl/param). $R = 0.083$, $R_w = 0.089$, $w = \sin\theta/\lambda$, $S = 4.24$. Maximum and minimum peaks of the final difference Fourier map: 0.79 and −0.39 e Å^{-3}; these residual electron densities could not be assigned to any chemically sensible moiety. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-239984. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: int. code +(44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

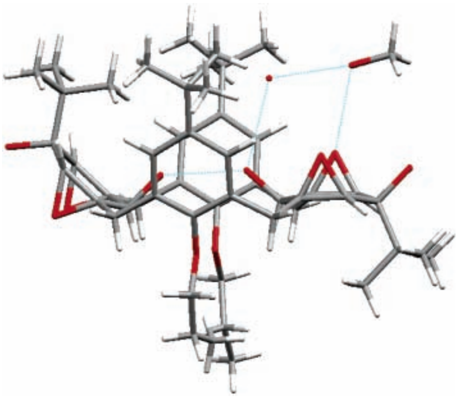

Figure 3. X-ray crystal structure of tetraepoxytetrol **7a**. The dashed lines represent H-bond interactions.

adopts a cone conformation with the *N*-ring in an *out* orientation, almost coplanar with the mean plane of the $ArCH_2$ carbons (interplanar angle of 1.9°). All the hydroxyl groups present in the molecule are engaged in H-bonds: the two tertiary alcoholic oxygens, pointing toward the exterior of the molecule, are involved in intermolecular H-bonds with epoxy oxygens of screw related molecules (the distance between the oxygens is 2.78 and 2.89 Å). The two secondary OH oxygens are 2.75 Å distant from each other. The one on the *N*-ring could act at the same time as a hydrogen donor to the other alcoholic oxygen on the *X*-ring and as an acceptor from a water molecule, which is 2.86 Å distant. The angle among these three oxygens is 107.8°, and the $C{-}O{\cdots}OH_2$ angle is 115.3°. The same water molecule is also 2.63 Å distant from the oxygen atom of a methanol molecule, which in turn is interacting with one epoxy oxygen (2.92 Å). The angle that the water oxygen forms with the two other ones is 112.8°.

Interestingly, this arrangement of H-bonds explains the shielding experienced by secondary OH on *N*-ring (1.85 ppm) with respect to that of the *X*-ring (4.67 ppm), indicating a strong and persistent H-bond in solution.

It is worth noting that the reduction of the *X*-ring in **6** proceeded with complete *exo* stereoselectivity, while that of the *N*-ring underwent both *exo* and *endo* attack. This could be explained by the flattened-cone orientation of the *N*-ring, observed in the MM3-minimized structure of **6** (Figure S12, Supporting Information), which would allow the hydride attack from both faces.

In conclusion, we have described a procedure for the easy introduction of oxygenated functions into the calixarene aromatic walls to give the first examples of epoxy-*p*-quinol and diepoxy-*p*-quinol calixarene derivatives. As observed for other calix[4]arene systems,[2,5,14] both the oxygenation and the subsequent carbonyl reduction occur with a preferential attack to the less hindered *exo* face of the calixarene rings. The *cis* configuration of hydroxy and epoxy groups of diepoxy-*p*-quinol system, previously supposed on the basis of mechanistic considerations,[7] is proved by X-ray analysis. The extension of oxygenation to a larger number of phenol rings and the utility of diepoxy-*p*-quinol derivatives as intermediates for the preparation of new hosts with a polar cavity, by epoxide ring-opening reaction with strong nucleophiles, are currently under study.

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Supporting Information Available: Synthetic details, $^{1}H/^{13}C$ and 2D NMR data, MM3 energy-minimized structure for **2**−**4**, **6**, and **7** (Tables S1−S3 and Figures S1−S22). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst*. **1999**, *32*, 115.

(14) Wöhnert, J.; Brenn, J.; Stoldt, M.; Alesiuk, O.; Grynszpan, F.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1998**, *63*, 3866.