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Convergent Synthesis of *p*-Benzylcalix[7]arene: Condensation and UHIG of *p*-Benzylcalix[6 or 8]arenes

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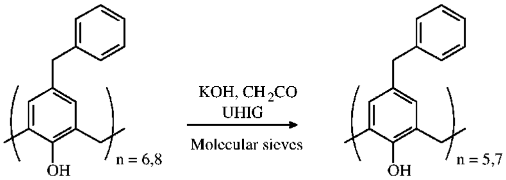
ABSTRACT



***p*-Benzylcalix[5]arene and *p*-benzylcalix[7]arene are formed on ultrahigh intensity grinding (UHIG) of *p*-benzylcalix[6 or 8]arenes in the presence of KOH and molecular sieves (4 Å), and the same calix[7]arene is also formed on condensation of *p*-benzylphenol and formaldehyde (15–20% yield), under more forcing conditions, along with *p*-benzylcalix[10]arene.**

Calixarenes are an extensively studied class of compounds, and their syntheses from *p*-substituted phenols (usually *tert*-butylphenol) and formaldehyde in the presence of base are well-established.[1] Despite this, the reasons for the formation of a particular calixarene are currently not well understood.[1,2] Even numbers of phenol units are usually favored in one-pot syntheses,[1] although theoretical studies indicate that odd-numbered calix[5,7]arenes are not destabilized compared with even numbered calix[4,6]arenes.[3] The base equivalent used during the syntheses usually predetermines the ring number, although calix[4]arenes are regarded as the thermodynamically favored product while calix[8]arenes are formed under kinetic control.[4]

While the milling of materials has been widely used for particle size reduction, mixing, or blending in the ceramic and powder metallurgy industries, ultrahigh intensity grinding (UHIG) has accomplished mechanical alloying,[5] reduction of metal chlorides,[6] activation of mixed oxides,[7] the transformations of polymeric materials,[8] and the degradation of pesticides.[9] There have been few applications of mechanochemistry at the molecular reaction level.[10] Herein we report the use of UHIG of *p*-benzylcalix[6,8]arene in a vibratory ball−mill as a strategy to gain access to *p*-benzylcalix[5]-arene in a solvent free solid-state procedure, beyond that derived from the condensation of *p*-benzylphenol with

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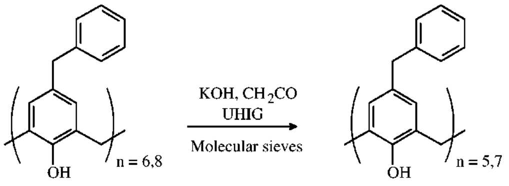
formaldehyde alone.[11−13] In the course of ball−milling these calixarenes and generating the calix[5]arene in 10−15% yield, we noted the formation of 5−10% of a new calixarene which was shown to be *p*-benzylcalix[7]arene, which was subsequently prepared in gram quantities by the direct reaction of *p*-benzylphenol with formaldehyde under more forcing conditions. Access to additional *p*-benzylcalix[5]arene alone is noteworthy as this calixarene can be used to selectively bind C_{60} from fullerite mixture;[12,13] this is related to the complementarity of curvature of the calixarene with that of C_{60}, along with symmetry considerations.[14,15] There are only a few reports on the synthesis of calix[7]arenes.[16,17] In addition, we have also isolated the corresponding calix[10]arene from condensation reactions, noting that the *p-tert*-butylcalix[10]arene has recently been reported.[18]

Base-catalyzed condensation of *p*-benzylphenol and formaldehyde leads to a mixture of *p*-benzylcalix[5,6,8]arenes in 33%, 16%, and 12% yields, respectively, with no evidence for formation of the calix[4 or 7]arenes.[11] Following the removal of the *p*-benzylcalix[5]arene, the subsequently purified calix[6 or 8]arenes were ball−milled with paraformaldehyde and KOH in the presence of molecular sieves (4 Å), Scheme 1. The product mixtures were extracted and the calix[5 and 7]arenes separated from starting material by chromatography.[19] Similar experiments with *p-tert*-butylcalix[6 and 8]arene yielded only starting materials. Variations of the UHIG conditions described above, however, result in only traces of the calix[5 and 7]arenes. Furthermore, calixarenes can be synthesized using UHIG from paraformaldehyde, base, molecular sieves, and *p*-benzylphenol, however only in trace amounts. These findings suggest that the products are not formed through a simple disproportonation mechanism.

Scheme 1



The collisions during UHIG, by means of compression, can give rise to local temperatures well beyond 500 °C.[20] It's noteworthy that the reported syntheses of other calix[5 and 7]arenes requires high temperatures.[11,16,17] Assuming a thermally driven process, in an adapted synthesis for *p*-benzylcalixarenes,[21] the temperature was ramped from 80 to 205 °C in under 3 min yielding *p*-benzylcalix[5, 7, and 10]arenes in 18−20%, 15−20%, and <5%, respectively. Variations of the KOH equivalents and increasing the ramping time resulted in lower yields or an absence of *p*-benzylcalix[7]arene in the reaction product mixture, suggesting that the quick ramp time is necessary for the production of *p*-benzylcalix[7]arene.

The solid-state structure of *p*-benzylcalix[7]arene was determined by X-ray crystallography.[22] The molecule adopts a pinched conformation, Figure 1, similar to the conformation observed for *p*-ethylcalix[7]arene (ignoring the benzyl and ethyl groups respectively)[23] but different from that of *p-tert*-butylcalix[7]arene;[24] the former has two of the seven hydroxy groups inverted with respect to the others, appearing

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(19) UHIG synthesis of the *p*-benzylcalix[7]arene was carried out in a stainless steel vial with a charge ratio, C_r, of 10 (mass of steel ball/mass of powder mixture),[25] under an argon atmosphere. Typically 0.6 g of a mixture of pure *p*-benzylcalix[6 or 8]arene, 0.2 g of KOH, 0.6 g of 4 Å molecular sieves, and 0.2 g of paraformaldehyde were ball milled for 4−16 h using a Spex 8000 Mixer- Miller. The product mixture, containing unreacted material, was extracted with $CHCl_3$, washed with 1.0 M HCl, and water, and then the organic fraction was dried with $MgSO_4$. *p*-Benzylcalix[5 and 7]arenes were separated as white powders by chromatography (SiO_2, eluent CH_2Cl_2/hexane 30/70), yields 10−15% and 5−10%, respectively. Similar yields were obtained by refluxing diphenyl ether solutions *p*-benzylcalix[6 or 8]arene, KOH (0.09 equiv/monomer), and paraformaldehyde (1 equiv/monomer) for 24−36 h. *p*-Benzylcalix[7]arene: mp 320 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 3.81$ (s-br, 4H; Ar-CH$_2$-Ar and Ph-CH$_2$-Ph), 6.88 (s, 2H; Ar-H), 7.21 (m, 5H; Ar-H), 10.31 (s-br, 1H; OH); MS (ESI) *m/z* (%) 1413 (100) [M•K$^+$]; $C_{98}H_{84}O_7$ (1373.8) calcd C 85.68, H 6.16; found C 85.45, H 6.18. Crystals were grown by vapor diffusion of MeOH into a toluene solution of *p*-benzylcalix[7]arene.

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(21) Synthesis of *p*-benzylcalix[7]arene: 9.72 g of *p*-benzylphenol and 4.50 g of paraformaldehyde were suspended in 65 mL of tetralin in a 250 mL RBF fitted with a Dean−Stark apparatus under N_2. The mixture was heated to 80 °C, then 0.35 mL of 14 M KOH was added, the temperature was quickly ramped (<3 min) and maintained at 205 °C for 4 h and thenthe solution dried with sodium sulfate, and the solvent was removed in vacuo. Addition of warm acetone (80 mL) yielded a white precipitate of *p*-benzylcalix[8]arene (12%).[11] Evaporation of the solvent under vacuum, followed by further addition of acetone (50 mL). yielded a white precipitate of *p*-benzylcalix[5]arene.[11] This final procedure was repeated to obtain a second crop of *p*-benzylcalix[5]arene upon standing for 24−48 h (15−20%). Further standing (1−3 days) yielded crystalline *p*-benzylcalix[7]arene (15−20%). Evaporation of the solvent under vacuum, followed by addition of acetone (40 mL) and standing at −30 °C for 2−5 days, yielded a white precipitate of *p*-benzylcalix[6]arene.[11] Further standing (1−2 days), after collection of *p*-benzylcalix[6]arene, yielded a white precipitate consisting of *p*-benzylcalix[5, 7, and 10]arenes which were separated by chromatography (SiO_2, eluent CH_2Cl_2/hexane 20/80), yield of *p*-benzylcalix[10]arene <5%. *p*-Benzylcalix[10]arene: mp 280 °C (dec); ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C, TMS) $\delta = 3.78$ (s, 2H; Ar-CH$_2$-Ar), 3.79 (s, 2H; Ph-CH$_{-}$Ph), 6.87 (s, 2H; Ar-H), 7.20 (m, 5H; Ar-H), 9.35 (s, 1H; OH); MS (ESI) *m/z* (%) 2001 (100) [M•K$^+$]; $C_{98}H_{84}O_7$ (1373.8) calcd C 85.68, H 6.16; found C 85.61, H 6.19%.

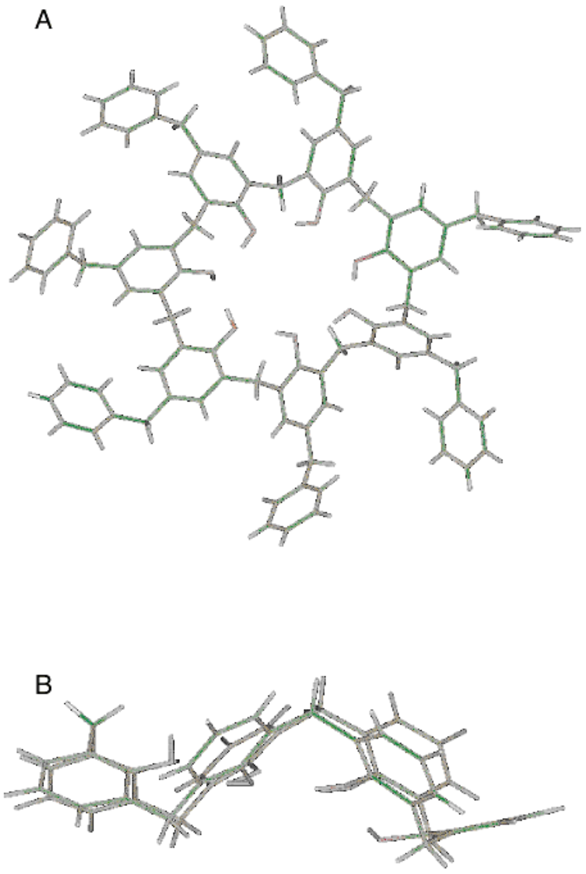

Figure 1. Structure of *p*-benzylcalix[7]arene showing (a) the C_1 symmetry (or close to C_s symmetry, ignoring the benzyl groups) [only one of the two disordered positions are shown for the benzyl groups] and (b) the pinched conformation (the benzyl groups have been omitted for clarity).

relatively flat in projection, while the latter shows a full complement of intramolecular hydrogen bonds on the same side of the hydrocarbon macrocycle.[24]

The structure of the *p*-*tert*-butylcalix[7]arene is consistent with the most stable conformation reported by Shinkai and Harada from MM3(92) calculations.[3] The conformation adopted by the *p*-benzylcalix[7]arene and *p*-ethylcalix[7]-arene, however, was reported in the same study to be unstable, corresponding to the 19th most stable conformation. The packing arrangement of the latter two are quite distinct, suggesting that the adopted conformation is not necessarily driven by crystal packing forces. Rather, the observed pinched conformation aims at maximizing the intramolecular hydrogen bonding network of the phenolic groups and minimizing steric crowding between the aryl-CH_2-aryl and hydroxy groups.[3] Strong intramolecular hydrogen bonding is evident in the solid state with all O···O distances between 2.60 and 2.74 Å. Furthermore, the IR spectra shows ν_{O-H}(KBr) at 3142 cm^{-1} (cf. 3138, 3229, and 3157 cm^{-1} for *p*-*tert*-butylcalix[4]arene,[1] *p*-benzylcalix[5]arene,[11] and *p*-benzylcalix[6]arene, respectively) which is also consistent with a strongly hydrogen bonded conformation.

The ^1H NMR spectra for *p*-benzylcalix[7]arene at 20 °C show a broad singlet at δ 10.31 ppm for the phenolic protons with no AB-system observed for the bridging methylene groups. At low temperature (−80 °C) the calix[7]arene adopts C_1 symmetry (cf. pseudo C_s in the solid state) which is apparent from the appearance of seven singlets for the hydroxy groups (δ 9.80−11.05 ppm), Figure 2, while the methylene groups are observed to coalesce at around 0 °C. This downfield shift is consistent with the formation of a stronger hydrogen bonded network at the lower temperature.

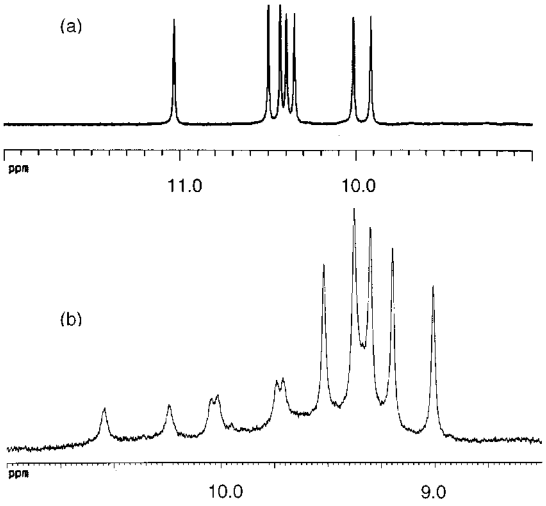

Figure 2. (a) ^1H NMR of hydroxy region of *p*-benzylcalix[7]arene and (b) *p*-benzylcalix[10]arene at 20 °C.

The ^1H NMR of the *p*-benzylcalix[10]arene show a sharp singlet at δ 9.35 ppm for the phenolic proton (20 °C) with no AB-system observed for the bridging methylene groups.

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(22) **Crystal Structure Determination for [*p*-Benzylcalix[7]arene]-$[CHCl_3]_{1.5}[H_2O]_{1.5}$:** $C_{99}H_{88.5}Cl_{4.5}O_{8.50}$, $M_r = 1573.72$, monoclinic, $P2_1/c$ (No. 14), $a = 16.47(9)$, $b = 21.8070(12)$, and $c = 25.4417(14)$ Å, $\gamma = 103.876(1)°$, $V = 8871(5)$ Å^3, $T = 123(1)$ K, $\rho_{calc} = 1.178$ g cm^{-1}, $\mu = 0.204$ cm^{-1} (no correction), $Z = 4$, Mo Kα radiation, 15492 unique reflections ($R_{int} = 0.170$), $2\theta_{max} = 50°$ (6378 observed, $I > 2\sigma(I)$), 1082 parameters, no restraints, $R_1 = 0.1724$, $wR_2 = 0.4811$ (all data). Data were collected at 123(1) K on an Enraf-Nonius Kappa CCD diffractometer on a colorless crystal of dimensions 0.25 × 0.20 × 0.20 mm. The structure was solved by direct methods (SHELXS-97) and refined with a full matrix least-squares refinement on F^2 (SHELXL-97). The benzyl groups showed considerable positional disorder which could not be adequately modeled except for phenyl group C64−C69 which was modeled as being disordered over two sites. Four of the phenyls were refined as rigid bodies. Solvent molecules were modeled as $CHCl_3$ or disordered water. With the exception of the disordered phenyl group C64−C69 which was refined isotropically, all non-hydrogen atoms were refined anisotropically. Hydrogen atoms on the calixarene and chloroform molecules were included at calculated positions with a riding refinement. The high residual values obtained are a consequence of poor crystal quality, weak data (41% observed), and the inherent disorder of the system and are in keeping with other structure determinations of higher calixarenes.[24]

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At low temperature (−80 °C), however, the calix[10]arene adopts two distinct conformations, from consideration of the hydroxy region of the ^{1}H NMR spectrum, Figure 2. The dominating species gives rise to five sharp peaks (δ 9.0−9.6 ppm), each integrating for two protons, suggesting that the adopted conformation has a mirror plain of symmetry (a similar pattern of peaks is observed for *p*-*tert*-butylcalix[10]arene).[18] The second conformation is considered to have C_1 symmetry by the appearance of eight equally integrating singlets (δ 8.8−10.6 ppm), the other two hidden under two singlets of the dominant species (from integration considerations).

Our findings demonstrate the use of UHIG in converting two even-numbered calixarenes (either 6 or 8) into uneven-numbered calixarenes (5 and 7) and the formation of the new *p*-benzylcalix[7 and 10]arenes which have interesting possibilities in supramolecular chemistry.

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Supporting Information Available: Crystal data, structure refinement details, and CIF file for *p*-benzylcalix[7]arene. This material is available free of charge via the Internet at http://pubs.acs.org

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