## SILVANOLS: WATER-SOLUBLE CALIXARENES

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Summary: The synthesis of calixarenes possessing a water-solubilizing arborol surface on the upper rim is reported. The "cone" isomer for calix[4]arene 5a is confirmed by X-ray crystal data.

Calixarenes,<sup>2</sup> which are  $[1_n]$  metacyclophanes, are practically insoluble in water; thus the reported<sup>3</sup> attachment of polar functionality has been a welcome addition to circumvent this limitation. Earlier we synthesized a series of arborols,<sup>4</sup> which when attached to hydrophobic materials instilled enhanced water solubility. We herein report the melding of the calixarene framework with that of arborol surface functionalization to generate a molecular "yose-uye" or silvanol.<sup>5,6</sup>

The key starting calixarenes were prepared following the general procedures devised by Gutsche et al.;<sup>2</sup> thus, treatment of 1 (prepared from *p-tert*-butylphenol) with AlCl<sub>3</sub> and phenol in toluene afforded the corresponding de-*tert*-butylated calixarene 2 in reasonable yields.<sup>7</sup> Acid catalyzed treatment<sup>7</sup> of 2a with formaldehyde and dimethylamine afforded (69%) 3a [mp 160 °C (dec)],<sup>8</sup> which after quaternization with methyl iodide, was treated with triethyl methanetricarboxylate<sup>9</sup> to give (87%) the crystalline dodecaester 4a.<sup>10</sup> Similarly, reaction of 2b with formaldehyde and diallylamine under acidic conditions gave (50%) the octaamine 3b [mp 100 °C (dec)].<sup>7</sup> After addition of methyl iodide, the intermediary ammonium salt was converted (25%) into the corresponding polyester 4b.<sup>11</sup> These phenolic calixarenes 4 were smoothly transformed in good to excellent yields into the corresponding *O*-methyl ethers (5).<sup>12</sup> The NMR spectra of 5 confirmed the symmetry, the completeness of conversions, and the appropriate 1:3 ratio of methyl groups.

In order to verify that the triester moieties were located on the upper rim, an X-ray crystal structure<sup>13</sup> of **4a** was conducted (see Figure 1). The four phenyl rings are nearly orthogonal with each neighbor (average angle:  $85 \pm 4^{\circ}$ ). The ester side chains are all on one side of the molecule and are nearly orthogonal to the best plane of each phenyl ring with opposite groups being external (91.78° and 92.96°) and internal (78.84° and 90.04°). Although high thermal parameters were exhibited for the ethyl ester substituents, one methyl group (C56) is strategically located within the molecular cavity and is nearly equidistant from the phenyl ring carbon



atoms (3.90  $\pm$  0.09Å). The four phenolic oxygens form a square due to *H*-bonding on the other side of the molecule.



Figure 1. Stereoview of the structure of 4a.

The second tier was constructed by treating **5a** with "tris" in the presence of anhydrous  $K_2CO_3$  in dry  $Me_2SO$  at 40 °C for 72 h to afford (89%) [36]-silvanol (**6a**),<sup>14</sup> as a pale yellow oil. Although the spectral data for **6a** are in accord with the assigned structure, an acceptable combustion analysis was not obtained due to the highly hygroscopic nature of **6a**; thus, the corresponding analytically pure acetate derivative (mp 68-70 °C) was

prepared. The [36]-silvanol can be quantitatively regenerated from this acetate by facile transesterification conditions (anhydrous  $K_2CO_3$  in absolute ethanol). The polyester **5b** was converted (92%) into [72]-silvanol (**6b**),<sup>15</sup> which possessed similar spectral and hygroscopic characteristics. The corresponding acetate was prepared, shown to be spectrally and analytically pure, then transformed back to the desired [72]-silvanol. Silvanols **6** are highly water soluble, and their aqueous solutions foam upon agitation.

The [36]-silvanol was directly imaged in the electron microscope<sup>16</sup> for size comparison with the predicted diameter from computer modeling<sup>17</sup> and to see if higher order structures are formed. At high

magnification  $(350,000\times)$ , small spheres and descrete aggregates can be seen (Figure 2). The predicted diameter for a single molecule of **6a** is ca. 27 Å; whereas, the smallest measured diameters (arrows) are 57 Å. However, molecular modeling of six interacting [36]silvanols (**6a**) predicts a sphere with an effective diameter of ca. 45-50 Å. The stain could account for the observed difference. The small spheres and the larger aggregates seen in Figure 2 may be a result of the experimental drying process before visualizing in the high vacuum of the electron microscope. Sylvanols may be monodispersed in an aqueous milieu, a point which is under active investigation.



Figure 2. Transmission electron micrograph of [36]-Silvanol; Bar =  $200\text{\AA}$ 

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## **References and Notes**

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- 10. mp 132-134 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.02 (t, J = 7.1 Hz,  $CH_3$ , 36H), 3.29-3.60 (m, ArCH<sub>2</sub>Ar, ArCH<sub>2</sub>, 16H), 4.10 (q, J = 7.1 Hz, OCH<sub>2</sub>, 24H), 6.96 (s, ArH, 8H), 9.89 (s, OH, 4H); <sup>13</sup>C NMR  $\delta$  13.3 (CH<sub>3</sub>), 31.4 (ArCH<sub>2</sub>), 37.6 (ArCH<sub>2</sub>Ar), 61.8 (OCH<sub>2</sub>), 66.4 (4°C), 127.8 (C4), 129.1, 131.3, 147.8 (C2,3,5), 166.5 (C=O); IR (KBr) 1740 cm<sup>-1</sup>; Anal. Calcd. (C<sub>72</sub>H<sub>88</sub>O<sub>28</sub>): C, 61.71; H, 6.29. Found: C, 61.80; H, 6.42.
- 11. mp 182-184 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.10 (t, J = 7.1 Hz,  $CH_3$ , 72 H), 3.37-3.95 (m, Ar $CH_2$ Ar, Ar $CH_2$ , 32 H), 4.08 (q, J = 7.1 Hz, OCH<sub>3</sub>, 48H), 7.04 (s, ArH, 16H), 9.5 (s, OH, 8H); <sup>13</sup>C NMR  $\delta$  13.39 (CH<sub>3</sub>), 31.47 (Ar $CH_2$ ), 37.62 (Ar $CH_2$ Ar), 61.69 (OCH<sub>2</sub>), 66.67 (4°C), 127.8 (C4), 128.9, 131.23, 148.11 (C2,3,5), 166.41 (C=O); IR (KBr) 1744 cm<sup>-1</sup>; Anal. Calcd (C<sub>144</sub>H<sub>176</sub>O<sub>56</sub>): C, 61.71; H, 6.29. Found: C, 61.87; H, 6.37.
- 12. **5a**: mp 60-62 °C; 92% yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.21 (t, J = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>, 36H), 3.29-3.90 (m, ArCH<sub>2</sub>, ArOCH<sub>3</sub>, 28H), 4.18 (q, J=7.1Hz, OCH<sub>2</sub>, 24H), 6.73 (s, ArH, 8H); <sup>13</sup>C NMR  $\delta$  13.4 (OCH<sub>2</sub>CH<sub>3</sub>), 30.4 (ArCH<sub>2</sub>), 37.9 (ArCH<sub>2</sub>Ar), 59.9 (OCH<sub>3</sub>), 61.43 (OCH<sub>2</sub>), 66.5 (4°C), 128.6 (C4), 130.9, 133.4, 156.9 (C2,3,5), 166.4 (C=O); IR (KBr) 1750 cm<sup>-1</sup>; Anal. Calcd (C<sub>76</sub>H<sub>96</sub>O<sub>28</sub>): C, 62.63; H, 6.64. Found: C, 62.45; H, 6.71. **5b**: oil; 82% yield; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.17 (t, J=7.1Hz, OCH<sub>2</sub>CH<sub>3</sub>, 72H), 3.37-3.87 (m, ArCH<sub>2</sub>Ar, ArCH<sub>2</sub>C), 32H), 3.99 (s, ArOCH<sub>3</sub>, 24H), 4.13 (q, J=7.1Hz, OCH<sub>2</sub>, 48H), 6.84 (s, ArH, 16H); <sup>13</sup>C NMR  $\delta$  13.46 (OCH<sub>2</sub>CH<sub>3</sub>), 29.81 (ArCH<sub>2</sub>), 37.73 (ArCH<sub>2</sub>Ar), 60.10 (OCH<sub>3</sub>), 61.45 (OCH<sub>2</sub>), 66.22 (4°C), 130.20, 130.74, 132.96, 155.34 (ArC), 165.85 (C=O); IR (neat) 1744 cm<sup>-1</sup>; Anal. Calcd. (C<sub>152</sub>H<sub>192</sub>O<sub>56</sub>): C, 62.63; H, 6.64. Found: C, 62.38; H, 6.93.
- 13. Crystal data for **4a**:  $C_{72}H_{88}O_{28}$ ,  $M_r = 1401.5$ , monoclinic, **P1**, a = 13.756 (2), b = 13.782 (3), c = 20.744 Å,  $\alpha = 85.69$  (2),  $\beta = 76.59$  (2),  $\gamma = 69.78$  (2)°, V = 3590 (2) Å<sup>3</sup>, Z = 2,  $D_c = 1.297$  g cm<sup>-1</sup>, F(000) = 1488, T = 292 K. Colorless crystals (ether), dimensions 0.23 x 0.40 x 0.62 mm, R = 0.071 for 8400 observations with I >  $3\sigma$ (I) of 14214 unique data.
- oil; <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 31.55 (ArCH<sub>2</sub>), 40.40 (ArCH<sub>2</sub>Ar), 60.88 (CH<sub>2</sub>OH), 61.89 (OCH<sub>3</sub>), 62.37 (CNH), 79.34 (4°C), 129.50 (C4), 133.82, 157.04, 159.2 (C2,3,5), 170.8 (C=O); IR 1680 cm<sup>-1</sup>. Acetate: mp 68-70 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.07 (s, COCH<sub>3</sub>); IR (KBr) 1752 (COCH<sub>3</sub>), 1680 (CON) cm<sup>-1</sup>; Anal. Calcd (C<sub>172</sub>H<sub>228</sub>N<sub>12</sub>O<sub>88</sub>): C, 53.36; H, 5.94; N, 4.34. Found: C, 53.16; H, 6.02; N, 4.12.
- oil; <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ 30.92 (ArCH<sub>2</sub>), 40.40 (ArCH<sub>2</sub>Ar), 60.93 (CH<sub>2</sub>OH), 61.91 (OCH<sub>3</sub>), 62.43 (CNH), 79.28 (4°C), 127.79, 133.71, 151.25, 159.25 (ArC), 170.77 (C=O); IR (neat) 1660 cm<sup>-1</sup>. Acetate: mp 102-104 °C; 80% yield; <sup>1</sup>H NMR δ 1.96 (s, COCH<sub>3</sub>); IR 1754 (COCH<sub>3</sub>), 1665 (CON) cm<sup>-1</sup>; Anal. Calcd (C<sub>344</sub>H<sub>456</sub>N<sub>24</sub>O<sub>176</sub>): C, 53.36; H, 5.94; N, 4.34. Found: C, 53.56; H, 6.07; N, 4.24.
- 16. Silvanol 6b was pipetted onto a formvar-coated grid, stained with 2% phosphotungstic acid (pH = 6.8), air dried, and viewed in a JOEL 100-CX TEM electron microscope at an accelerating voltage of 80 kV.
- 17. Calculations were performed on a Silicon Graphics IRIS 4D/50GT superworkstation with the use of Polygen's QUANTA/CHARMm software; see: B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, and M. Karplus, J. Comput. Chem., 4, 187 (1983).

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