C_4 dissymmetric resorcinarene derivatives: Synthesis, crystal structure and micelle formation

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Abstract

The synthesis of a C_4 dissymmetric resorcinarene tetracarboxylic acid derivative and determination of its critical micelle concentration is reported. The tetrahydroxy derivative was prepared by reduction of the tetra-acid. The low-temperature single crystal X-ray structure of the methyl ester derivative of the tetra-acid is also reported. This crystallised with two independent molecules of similar boat (flattened cone) conformation within the asymmetric unit.

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Keywords Crystal structure, resorcinarene, C_4 dissymmetry, micelles

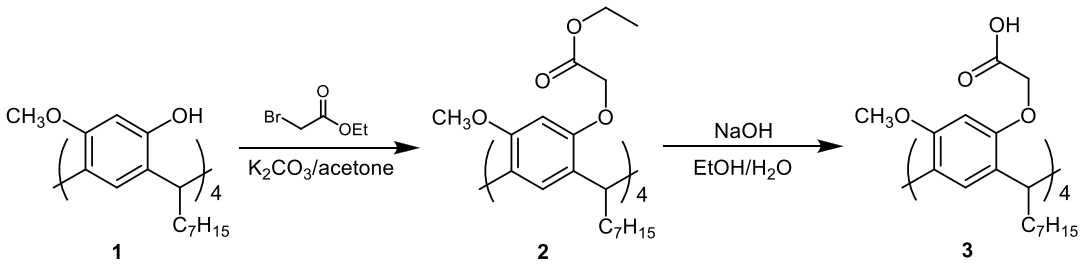
Dedicated to Professor Jack Harrowfield on the occasion of his 70th birthday.

Introduction

Resorcinarenes and calixarenes are phenol-based cyclophanes that have been investigated for potential applications in a variety of fields including biology [1], separation science [2], surface science [3] and sensors [4]. The synthesis and properties of chiral calixarenes have also attracted significant interest [5, 6]. The surfactant properties of many calixarene and resorcinarene derivatives have also been investigated [7-10] and their chiral forms have found a variety of applications. These include chiral capillary electrophoresis [11, 12], enantioselective reduction of prochiral ketones with sodium borohydride [13] and enantio-discriminating n.m.r. solvent additives [14].

Results and discussion

The reaction of an α–haloester such as ethyl bromoacetate with resorcinarenes [15, 16] and calixarenes [17, 18] is a frequently applied methodology for incorporation of a 'flexible' functional group. The tetraethyl ester (**2**) was prepared according to the previously published method [19], by the reaction of **1** [20] (Scheme 1) with ethyl bromoacetate and anhydrous potassium carbonate. All spectroscopic data matched the published values [19].



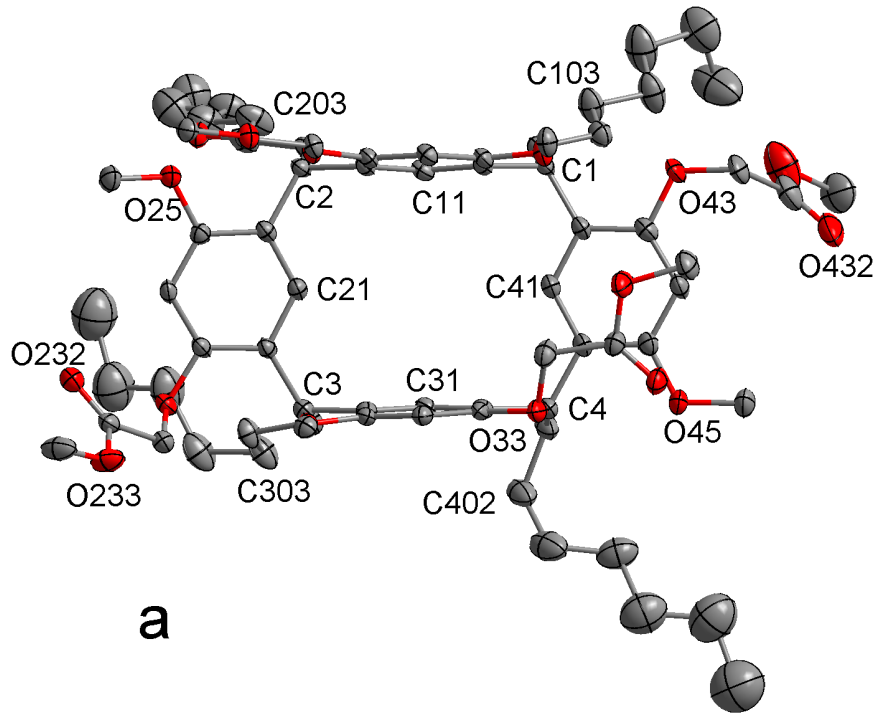
Scheme 1 Synthesis of the resorcinarene tetra-ester **2** and tetra-acid **3**

A single crystal suitable for a single crystal X-ray study was obtained by slow evaporation of a methanol - dichloromethane solution of **2**. Somewhat surprisingly, the structure was determined to be in fact, that of the tetra-methyl, rather than the expected tetra-ethyl, ester (Fig. 1). We presume its formation to be due to a trace of acid in the methanolic crystallisation medium, causing gradual transesterification, the equilibrium of which may have been driven by the tetra-methyl ester being less soluble in that solvent mixture. The methanolic crystal growing solution of **2** was stable for approximately one week before crystallisation occurred. Suitable crystals of **2** could not be obtained as it would not crystallise favourably from any other solvent (including ethanol based) mixtures.

*Structure and properties of **'2'***

The single crystal X-ray study shows the compound to be unsolvated, two molecules, devoid of crystallographic symmetry and in a non-polar space group, comprising the asymmetric unit of the structure; as described above the compound is the tetra-methyl, rather than the tetra-ethyl ester. The two molecules are very similar in conformation (boat or flattened cone); the pairs of phenyl rings comprising the 'basal plane' have interplanar dihedral angles of 19.9(1), 15.8(1)º (mols. 1,2), while those between the 'parallel' 'uprights' are 10.5(1), 25.1(1)º, there being an appreciable divergence of the pair in the latter case. The

dispositions of the ring and bridge substituent 'tails' are diverse (**Fig**. **1**), with no evident inclusion of neighbouring substituents within the pairs of 'upright' planes



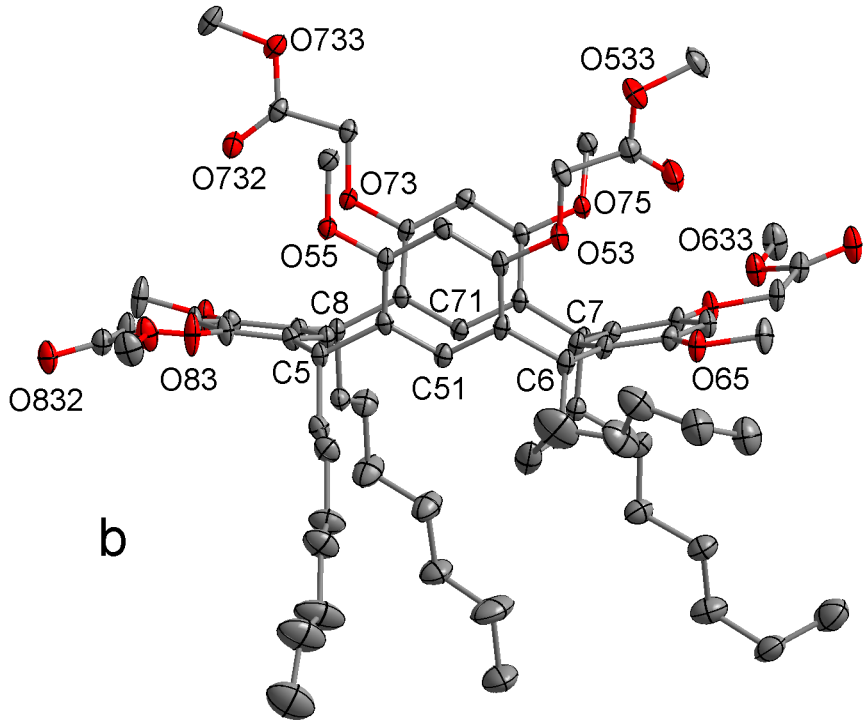


Fig. 1 Projections of the two molecules of **2** (*C*-heptyl-tetramethoxycalix[4]resorcinarene tetramethyl-ester), **a** down (mol. 1) and **b** normal (mol. 2) to their molecular 'axes'. Minor components of the disordered atoms and hydrogens have been omitted.

Hydrolysis of the ester to the tetra-acid **3** (Scheme 1) proceeded smoothly in the presence of sodium hydroxide/methanol/water. Hydrolysis with sodium hydroxide/water alone was very slow due to the lipophilicity of **2**. The ^{13}C n.m.r. spectrum of the tetra-acid (**3**) showed only one signal for the methyleneoxy carbon (at δ 67.7) and in the proton n.m.r. spectrum no signals were observed for the ethoxy protons of the starting material. The tetra-acid was significantly soluble in alkaline solution and demonstrated a potential for application as a surfactant. To that end it was deemed prudent to evaluate the critical micelle concentration (CMC) of the model racemic surfactant with a view to future use of the enantiopure acid.

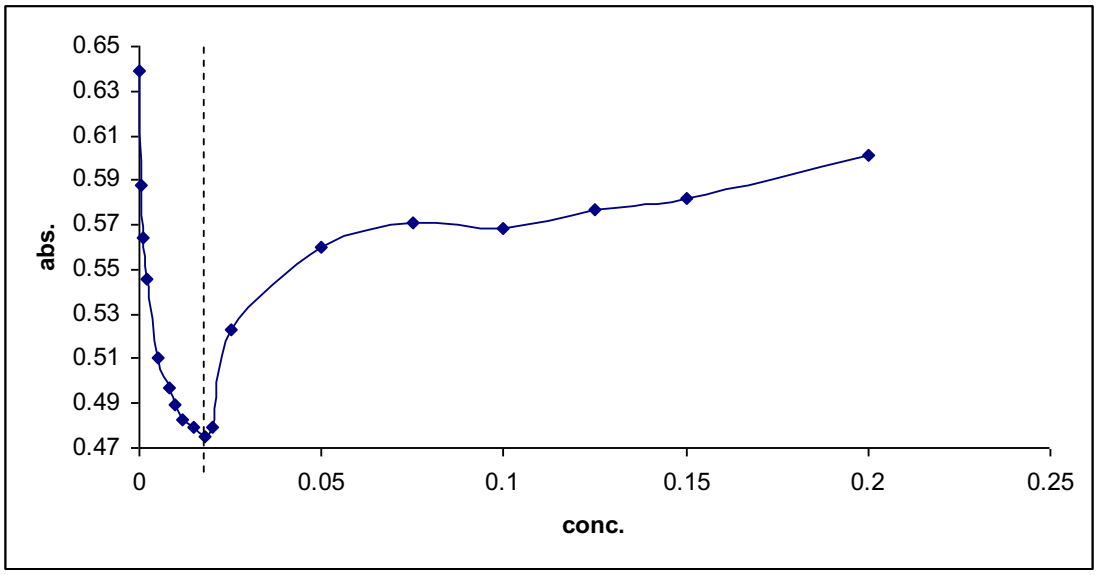
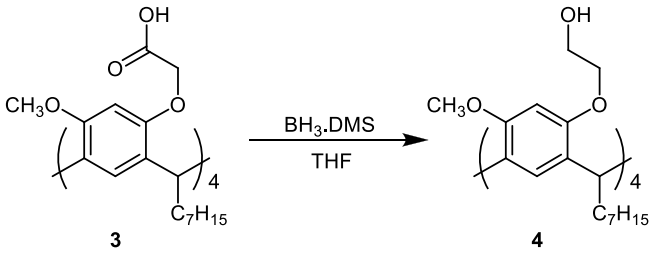


Fig. 2 Plot of concentration (mol L^{-1}) of **3** vs absorbance of methylene blue indicator.

Determination of the UV-vis absorbance for methylene blue indicator [21, 22] at a range of concentrations of tetra-acid **3** revealed a CMC of approximately 1.8 x 10^{-2} mol L^{-1}. This value is reasonable considering the resorcinarene alkyl chains are comparatively short when compared to typical anionic surfactants such as sodium dodecyl sulfate (CMC ~ 5 x 10^{-3} mol L^{-1}). Also, the CMC is well known to increase with decreasing chain length [23]. The apparent decrease in absorbance prior to the CMC appears a result of some association of the methylene blue with the resorcinarene. Potentially this may be due to incorporation of the dye in the calix or the resorcinarene alkyl chains, but, no substantial evidence for this is available.



Scheme 2 Reduction of the tetra-acid **3** to the tetra-glycol ether **4**

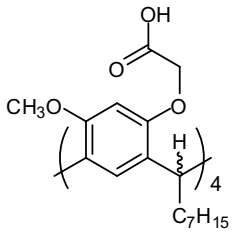
The tetrol **4**, readily obtainable by reduction of the tetra-ester **2** or the tetra-acid **3** has the potential for further functionalisation including the formation of crown ethers. Chiral crown ethers have been used for the enantioselective transport of amines [24], amino acids [25] and in chiral chromatography [26]. Reduction of the tetra-acid **3** with borane-dimethylsulfide afforded the tetrol in good yield. The ^{13}C n.m.r. spectrum of the tetrol (**4**) confirmed the reduction of the carboxylic acid with a pair of signals for the methyleneoxy carbons at δ 62.1 and 70.6 and the absence of any signal for a carbonyl carbon.

Unfortunately the solubility of the tetra-glycolether **4** in alkaline solutions proved to be too low for **4** to be effective as a surfactant.

Experimental

Melting points were determined on an Electrothermal 9100 apparatus. Nuclear magnetic resonance spectra were acquired on a Varian Gemini 2000 instrument at 200 MHz for proton and 50.3 MHz for carbon. Carbon assignments (where given) were made with the assistance of DEPT 135 and DEPT 90 experiments. Spectra are calibrated to their respective solvent signals: deuteriochloroform ($CDCl_3$, ^1H, δ7.27 ppm; ^{13}C, δ77.7); d_6-dimethylsulfoxide (CD_3SOCD_3, ^1H, δ2.50; ^{13}C, δ39.5). Infrared spectra were recorded on a a Bruker Vector 22 spectrometer. Mass spectra were recorded with a Jeol-SX102 using fast atom bombardment (FAB). Elemental microanalysis was carried out by the Central Science Laboratory, University of Tasmania, Australia. 2,4,6,8-Tetraheptyl-1^4,3^6,5^6,7^6-tetraethoxycarbonyl-methyleneoxy-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene (**2**)* was synthesised by alkylation of the resorcinarene (**1**) [20] with ethyl bromoacetate as described previously [19].

2,4,6,8- Tetraheptyl-1^4,3^6,5^6,7^6-tetramethylenecarboxy-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene (3)

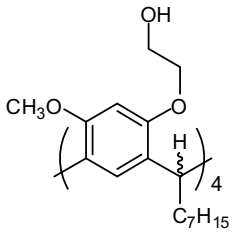


To a solution of the tetra-ester **2** (0.51 g, 0.40 mmol) in methanol (200 mL) and water (2 mL) was added sodium hydroxide (3.18 g, 80 mmol) and the mixture heated at reflux for 5 h. The solvents were then removed at reduced pressure to give a white solid to which was added hydrochloric acid (5M, 50 mL). The precipitate was collected by suction filtration and dried in a vacuum desiccator over phosphorus pentoxide for 72 h (0.43 g, 92 %). Recrystallisation of an analytical sample from methanol afforded colourless needles m.p. 84.0 - 85.0 °C. ^1H n.m.r.

* Calixarene nomenclature follows that recommended by IUPAC. See: Favre et al. [27] and McIldowie et al [5] for calixarene examples.

($CDCl_3$ + d_6-DMSO) δ 0.80 (br t, 12 H, CH_2CH_3), 1.10 - 1.35 (m, 40 H, $(CH_2)_5$), 1.70-1.90 (m, 8 H, CH_2CH), 3.60 (s, 12 H, OCH_3), 4.11, 4.27 (AB quartet, 8H, J = 15.9 Hz, OCH_2COO), 4.50 (t, 4 H, J = 7.4 Hz, $CHCH_2$), 5.98 (br s, 4 H, COOH), 6.24 (s, 4 H, ArH), 6.67 (s, 4 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.7 (CH_3), 23.2, 28.4, 30.0, 30.4, 32.6, 35.2, 35.7 (6 x CH_2 and CH), 56.4, 67.7 (OCH_3 and OCH_2COO), 99.0, 126.7, 127.5, 128.0, 154.7, 155.8 (6 x Ar) and 171.4 (C=O). HRMS (FAB): calcd. for $C_{67}H_{97}O_{14}$ $[M+H-CO_2]^+$ 1125.6878; found 1125.6844.

2,4,6,8- Tetraheptyl-1^4,3^6,5^6,7^6-tetra-(2-hydroxyethoxy)-1^6,3^4,5^4,7^4-tetramethoxyresorcin[4]arene (4)



To a solution of the tetra-acid **3** (0.50 g, 1.71 mmol) in dry tetrahydrofuran (10 mL) was added borane dimethylsulfide complex (1.71 mL, 10 M, 17.1 mmol). The mixture was stirred at room temperature for 2 h and then heated to reflux overnight. The remaining borane was quenched with methanol and the solvents removed at reduced pressure. The resulting mixture was treated with an excess of hydrochloric acid (3 M) and the resulting white solid recovered by filtration (463 mg, 97 %) essentially pure by n.m.r., m.p. 186 - 187 °C. ^1H n.m.r. ($CDCl_3$) δ 0.87 (br t, 12 H, CH_2CH_3), 1.15-1.39 (m, 40 H, $(CH_2)_5$), 1.74-1.92 (m, 8 H, CH_2CH), 2.50 (bs, 4 H, OH), 3.56 (s, 12 H, OCH_3), 3.62 – 4.00 (m, 16 H, OCH_2CH_2O), 4.51 (t, 4 H, J = 7.4 Hz, $CHCH_2$), 6.22 (s, 4 H, ArH), 6.78 (s, 4 H, ArH). ^{13}C n.m.r. ($CDCl_3$) δ 14.8 (CH_3), 23.4, 28.6, 30.0, 30.6, 32.7, 35.4, 35.9 (6 x CH_2 and CH), 56.9(OCH_3), 62.1, 70.6 (2 x OCH_2), 97.8, 126.7, 127.2, 127.6, 155.0, 156.0 (6 x Ar). Found: C, 73.4; H, 9.5; $C_{68}H_{104}O_{12}$; requires C, 73.3; H, 9.4 %.

Structure determination

A full sphere of CCD area-detector diffractometer data was measured (Bruker AXS instrument, ω-scans, $2\theta_{max} = 50^{\circ}$; monochromatic Mo K$\alpha$ radiation, $\lambda = 0.7107_3$ Å; T ca 150 K) yielding 50236 reflections, these merging to 24120 unique (R_{int} 0.064) after 'empirical'/multiscan absorption correction (12871 with $F > 4\sigma(F)$) and used in the full matrix least squares refinements, refining anisotropic displacement parameter forms for the non-hydrogen atoms, $(x, y, z, U_{iso})_H$ being included constrained at estimated values. Reflection weights were $(\sigma^2(F^2) + 8.4P)^{-1}$ ($P = (F_o^2 + 2F_o^2)/3$). Neutral atom complex scattering factors were employed within the context of the SHELXL 2014 program [28]. Pertinent results are presented below and in the Figures, the latter showing non-hydrogen atom displacement envelopes at the 30% probability level. CCDC **1050998.**

Crystal/refinement data

2. $C_{72}H_{104}O_{16}$, M = 1225.6. Triclinic, space group $P\bar{1}$ $(C_i^1, \text{No. } 2)$, a = 17.434(4), b = 19.362(4), c = 22.521(4) Å, α = 71.308(4), β = 78.867(4), γ = 75.918(4)º, V = 6930(3) Å^3. D_c (Z = 4) = 1.17_5 g cm^{-3}. μ_{Mo} = 0.082 mm^{-1}; specimen: 0.31 x 0.26 x 0.18 mm, $T_{min/max}$ = 0.87. $R1$ = 0.084, $wR2$ = 0.268; S = 1.026. Three pendant chains of each of the two independent molecules of the asymmetric unit were modeled as disordered, each over two sets of sites with concerted occupancies refining to 0.657(3) and its complement.

Conclusion

Two C_4 dissymmetric resorcinarene derivatives were synthesised and the critical micelle concentrations (CMC) of the tetra-acid **3** found to be 0.018 mol L^{-1}. The tetrol **4** was

insufficiently soluble to act as a surfactant. The low-temperature single crystal X-ray structure of the methyl ester derivative of tetra-acid **3** is also reported. Two molecules, both of similar conformation, the boat or flattened cone, were present in the unit cell.

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