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Formation of water-soluble sulfonated azacalix[4]arenes from cyanuric chloride

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ABSTRACT

Addition of cyanuric chloride **2** (2,4,6-trichlorotriazine) to 4,6-diaminobenzene-1,3-disulfonic acid **1** gives a bis-triazine **3** which may be cyclised with diaminoarenes to yield water-soluble azacalix[4]arenes **5a–d**. Alternatively, double substitution of chloride from the bis-triazine **3** yields new bis-triazine derivatives which may likewise be cyclised to functionalised azacalixarenes bearing functionalised side chains.

1. Introduction

Since their discovery by Baeyer,[1,2] and the pioneering work carried out by Zinke[3–6] and Gutsche[7] there has been an explosion of interest in the synthesis of calixarenes.[8] The incorporation of heteroatoms—particularly nitrogen—into calixarenes offers further sites for functionalisation and binding, amplifying the diversity of heterocalixarenes and resulting in a variety of new applications.[8]

For syntheses of azacalixarenes based on aza-aromatics such as pyridines or triazines, nucleophilic substitution or palladium-catalysed coupling chemistry in organic solvents has generally been employed to construct the macrocyclic ring.[9–16] Triazine-based macrocycles have shown to perform well in recognition studies, providing both hydrogen bond donor and acceptor sites for the selective binding of biological targets,[17] and linear routes to triazine-based azacalixarenes of various ring sizes have been described.[18–20]

In this Letter, we describe a related approach to water-soluble azacalixarenes involving the direct condensation of sulfonated aniline derivatives with cyanuric chloride **2** (2,4,6-trichlorotriazine) and its substitution products. Treatment of 4,6-diaminobenzene-1,3-disulfonic acid **1** with excess cyanuric chloride **1** at 0 °C in water and acetone at constant pH 6 gave a water-soluble bis-triazine **3** of limited stability (Scheme 1). When treated with a slight excess of diamines **4a–d** at pH 3.5, **3** was consumed in approximately 2 h—a significant rate increase relative to similar reactions in organic solvents.[20] On adding sodium carbonate solution to adjust the pH to 5.5, a precipitate was formed in each case which was identified by ^{1}H NMR and mass spectrometry as the azacalix[4]arenes **5a–d** (Scheme 1). The reactions with **4a** and **4b** gave clean azacalixarene products, but reactions with **4c** and **4d** gave significant quantities of apparently acyclic derivatives.

We hoped that functionalisation of the azacalixarene precursor **3** would improve the handling properties of the products. Bis-triazine **3** was therefore treated in situ with amines **6a–c** (Scheme 2). The reactions were carried out using a slight excess of amine (2.2 equiv) at room temperature in water and acetone. The pH of the reaction mixture was regulated by the addition of sodium carbonate solution and was adjusted according to the pK_a of the amine used in the reaction. After the reactions were complete the solutions were stirred at room temperature, at pH 5.5, for 2–4 h. The resulting slurries were then filtered giving compounds **7a–c** in high yield, with a high degree of purity.

Of the functionalised bis-triazines prepared, **7a** in particular showed improved solubility in water. All three derivatives **7a–c** were treated with 1.1 equiv diamines **4a** and **4b** for 2–3 h. After the reactions were complete, the reaction mixtures were cooled to 0 °C, and the pH was adjusted to 5.5. The products were isolated by filtration in moderate to good yields. With each of **7a–c**, cyclisation proceeded cleanly when *p*-phenylenediamine **4a** was used, yielding azacalixarenes **8a–c** in good yield (Scheme 2). Compound **7a** likewise reacted cleanly with *m*-phenylenediamine **4b** to form the azacalixarene **9a**. Compounds **7b, c** also cyclised with *m*-phenylenediamine **4b**, as indicated by mass spectroscopy, but the reaction mixture contained significant oligomeric impurities which were difficult to remove from the macrocyclic products **9b, c**, which were formed in relatively low yield.

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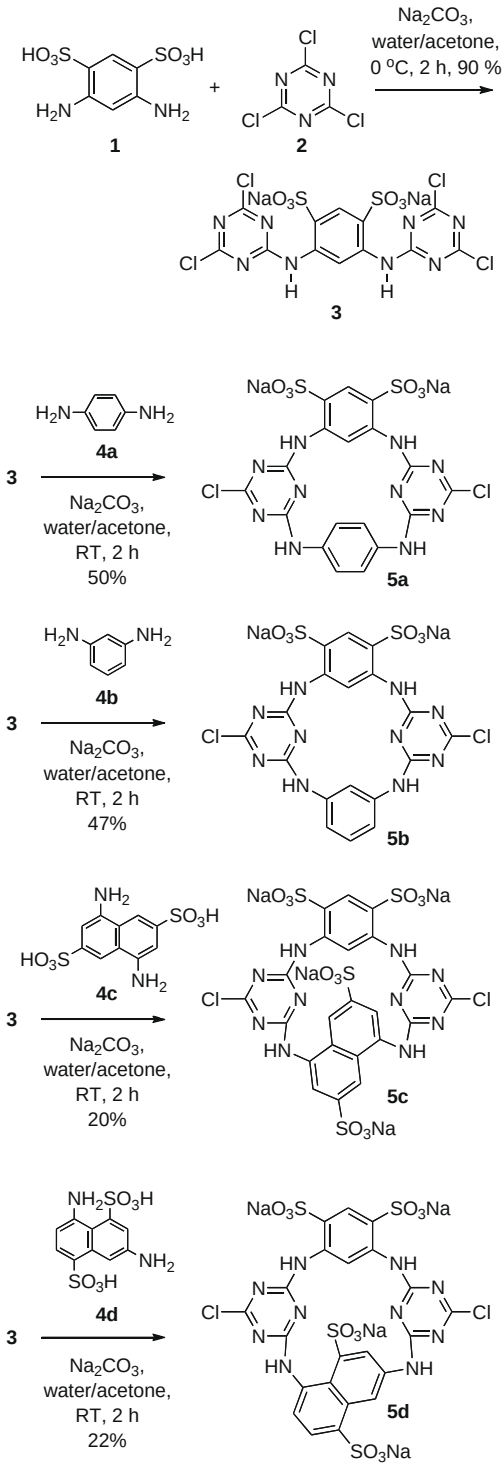
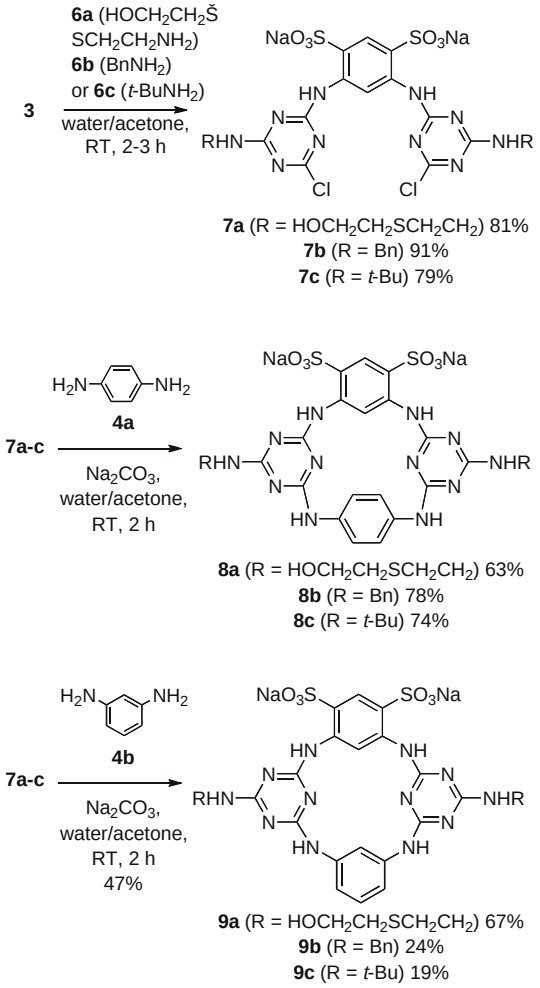


Scheme 1. Water-soluble azacalixarenes.



Scheme 2. Functionalised azacalixarenes.

In summary, we found that a range of bis-triazine derivatives of sulfonated diamine **1** can be cyclised simply on addition of a diaminobenzene in water, simplifying greatly previous syntheses of related azacalixarenes.

2. Experimental

Disodium 4,6-bis(4,6-dichloro-1,3,5-triazin-2-ylamino)benzene-1,3-disulfonate **3**: Cyanuric chloride (13 g, 70.4 mmol, 2.7 equiv) dissolved in acetone (100 ml) was slowly added to a solution of 4,6-diaminobenzene-1,3-disulfonic acid (7.3 g, 26.6 mmol, 1 equiv) dissolved in water (100 ml), at 0 °C. The pH of the reaction mixture was maintained at 6 by the addition of aqueous Na_2CO_3 (2 M). After 2 h the reaction was complete by HPLC, yielding the title compound in solution.

Tetraazacalix[2]arene[2]triazine **5a**: The solution of **3** was acidified (pH 3.5) by the addition of aqueous HCl (2 M). 1,4-Diaminobenzene (26.6 mmol) dissolved in water (200 ml) was slowly added at room temperature. The pH of the reaction mixture was maintained at 3.5 by the addition of aqueous Na_2CO_3 (2 M). After 2 h the reaction was complete by HPLC. The reaction mixture was basified (pH 5.5) and stirred for 1 h. The resulting slurry was filtered to give the title azacalixarene (8 g, 50%) as a grey powder, mp >300 °C; ν_{max}(KBr/cm^{-1}) 3328 (Ar-NH), 2950, 1413 (Ar-SO_2OH) and 1645, 1576 (Ar); δ_H (300 MHz; DMSO-d_6) 10.1 (2H, s, $(NH)_2$), 9.70 (2H, s, $(NH)_2$), 8.20 (1H, s, Ar-H), 7.18 (4H, s, Ar-H) and 6.85 (1H, s, Ar-H); δ_C (75 MHz; DMSO-d_6) 168.0, 167.3, 164.2, 136.2, 134.8, 134.4, 126.7 and 119.2; *m/z* (ES-) 298 (100%, M^{2-}).

Disodium 4,6-bis(4-(2-(hydroxyethylthio)ethylamino)-6-chloro-1,3,5-triazin-2-ylamino)benzene-1,3-disulfonate **7a**: The above-mentioned solution of **3** was adjusted to pH 7.5 by the addition of Na_2CO_3 (2 M). The amine (51.9 mmol, 2.2 equiv), dissolved in water (100 ml), was slowly added to the solution at room temperature, regulating pH at 7.5 by the addition of aqueous Na_2CO_3 (2 M). After 2–3 h the reaction was complete by HPLC. The pH of the reaction mixture was adjusted to 5.5 by the addition of HCl (2 M) and the mixture was stirred until the product precipitated

(typically in 2–4 h). The resulting slurry was filtered to give the title triazine (14 g, 81%) as a white powder, mp >300 °C; ν_{max}(KBr/cm^{-1}) 3330 (Ar-NH), 2940, 1415 (Ar-SO_2OH) and 1640, 1576 (Ar); δ_H (300 MHz; D_2O) 9.24 (1H, s, Ar-H), 8.18 (1H, s, Ar-H), 3.35 (4H, t, *J* 6.5, CH_2), 2.90 (4H, t, *J* 6.5, CH_2), 2.27 (4H, t, *J* 6.5, CH_2) and 2.15 (4H, t, *J* 6.5, CH_2); δ_C (75 MHz; D_2O) 168.7, 164.8, 163.0, 137.2, 127.1, 127.0, 115.5, 60.5, 41.1, 33.4 and 29.2; *m/z* (ES-) 733 (10%, M^-) and 755 (100, M+Na).

Tetraazacalix[2]arene[2]triazine **8a**: Disodium 4,6-bis(4-(2-(hydroxyethylthio)ethylamino)-6-chloro-1,3,5-triazin-2-ylamino) benzene-1,3-disulfonate **7a** (0.52 mmol) and 1,4-diaminobenzene (0.52 mmol) were dissolved in water (100 ml) at room temperature. The solution was acidified (pH 3.5) by the addition of aqueous HCl (2 M). The reaction mixture was heated to 80 °C. After 3 h the reaction was complete by HPLC. The reaction mixture was cooled to 0 °C, basified (pH 5.5) and stirred for 1 h. The resulting slurry was filtered to give the azacalixarene (0.3 g, 63%) as a grey powder, mp >300 °C; ν_{max}(KBr/cm^{-1}) 3328 (Ar-NH), 2941, 1414 (Ar-SO_2OH) and 1643, 1581 (Ar); δ_H (300 MHz; DMSO-d_6) 10.30 (2H, s, $(NH)_2$), 9.20 (2H, s, $(NH)_2$), 8.36 (1H, s, Ar-H), 8.30 (2H, s, $(NH)_2$), 6.95 (1H, s, Ar-H), 6.90 (4H, s, Ar-H), 3.64-3.50 (8H, m, $(CH_2)_4$), 2.80 (4H, t, *J* 6.9, $(CH_2)_2$) and 2.68 (4H, t, *J* 6.9, $(CH_2)_2$); δ_C (75 MHz; DMSO-d_6) 164.0, 157.3, 156.4, 155.7, 143.0, 134.6, 13.1.2, 127.6, 125.9, 61.6, 40.9, 34.5 and 31.0; *m/z* (ES-) 384 (100%, M^{2-}).

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