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Synthesis of a Capped Dicationic Derivative of β-Cyclodextrin

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Abstract: A derivative of β-cyclodextrin has been prepared in which the primary rim is capped by a linker containing two guanidinium groups. This compound is designed to serve as a highly preorganized host for aryl phosphate esters in aqueous solution.

Cyclodextrins (CDs) continue to play a preeminent role as host molecules for molecular recognition in aqueous solution. Introduction of appropriate functional groups on the rims of the CD cavity can be used to effect specific interactions with an included guest, providing an approach to increase both binding affinity and selectivity. We recently reported the synthesis of a β-CD derivative in which the primary hydroxyl groups of the A and D sugars are replaced with guanidinium groups.[1] Although this compound possesses moderate affinity for an aryl phosphate ester (phosphotyrosine) in aqueous buffer (K_a = 310 M^{-1}), significantly tighter binding will be required for use in biological systems, which is the ultimate objective of this work.[2] In principle, preorganizing this host by fixing the guanidinium groups over the CD cavity will lead to higher association constants with such guests. Here we report the synthesis of a macrobicyclic derivative of β-CD in which two guanidinium groups on the primary rim are covalently linked *via* a pentamethylene bridge.[3] Synthesis of this compound (**3**, Scheme 1) involved macrocyclization of diaminocyclodextrin **1** with 1,5-diisothiocyanato-pentane under high dilution to produce dithiourea **2**, alkylation of **2** with ethyl bromide, and reaction of the resulting diisothiuronium salt with ammonia. To our knowledge, **3** is the first example of a positively-charged capped cyclodextrin derivative.

The hydrogencarbonate salt of 6^A,6^D-diamine **1**[1,4,5] (414 mg) and 1,5-diisothiocyanatopentane[6] (78 mg) were each dissolved in 20 mL of DMF and the resulting solutions were taken up in separate 25 mL gas tight syringes. These solutions were simultaneously added *via* syringe pump over 6 h to 130 mL of DMF containing diisopropylethylamine (146 μL) at room temperature. The reaction mixture was stirred an additional 96 h at room temperature and concentrated *in vacuo*. The resulting viscous material was added to 200 mL of diethyl ether providing a white precipitate that was collected by filtration and applied to a (carboxymethyl)cellulose column (3" x 12"). Elution with aqueous ammonium bicarbonate (0 to 200 mM, 4 L total volume) provided dithiourea **2** (300 mg, 62%) after repeated lyophilization from water.[7] Ethyl bromide (200 μL), **2** (120 mg), and isopropanol (1 mL) were heated to 70 °C in a closed reaction vial for 23 h.[8] The reaction was allowed to cool, additional ethyl bromide (200 μL) was added, and the reaction was heated to 70 °C for 48 h. Volatiles were removed *in vacuo*, 2 M ammonia in isopropanol (4 mL) was added, and the resulting mixture was heated to 70 °C in a closed reaction vial for 24 h. The sample was then concentrated *in vacuo* and applied to a (carboxymethyl)cellulose column (3" x 12"). Elution with aqueous ammonium bicarbonate (0 to 200 mM, 4 L total volume followed by 2 L of 400 mM) provided the *bis*-bicarbonate salt of **3** (56 mg, 42%) after repeated lyophilization from water.[9]

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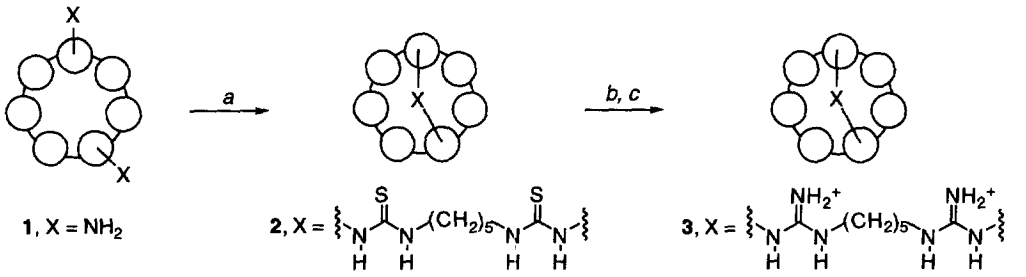

Scheme 1. *a*) $SCN(CH_2)_5NCS$, DIEA, DMF, RT (62%). *b*) EtBr, IPA, 70 °C. *c*) NH_3, IPA, 70 °C (42%, 2 steps). Note: In this scheme, each small circle represents a glucose unit in β-CD and X is covalently bonded to the primary carbon of the glucose indicated.

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7. Data for **2**: R_f = 0.32 (silica, 5:3:3:1 1-propanol:ethyl acetate:water:conc. NH_4OH). ^1H NMR (300 MHz, d_6-DMSO)[10] δ 7.4-7.1 (br m, 4 H), 6.05-5.45 (m, 14 H), 4.86-4.75 (m, 6 H), 4.5-4.2 (br m 6 H), 4.1-3.85 (br s, 2 H), 3.8-3.6 (m, 15 H), 3.4-3.3 (br s, 13 H), 3.3-3.2 (m, 19 H), 3.2-3.0 (br m, 4 H), 1.7-1.4 (br m, 4 H), 1.35-1.1 (br m, 2 H). MS (MALDI-TOF) *m/z* calcd for $M+Na^+$ 1341.4, measured 1341.8. Anal. calcd for $C_{49}H_{82}N_4O_{33}S_2 \cdot 5H_2O$: C 41.76%, H 6.58%, N 3.97%. S 4.55%. Found: C 41.82%, H 6.56%, N 4.06%, S 4.64%.
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9. Data for **3** (HCO_3^- salt): R_f = 0.21 (silica, 5:3:3:1 1-propanol:ethyl acetate:water:conc. NH_4OH). ^1H NMR (D_2O, 300 MHz) δ 5.13-5.06 (m, 7 H), 4.89-4.61 (m, 45 H), 4.00-3.79 (m, 26 H), 3.71-3.56 (m, 12 H), 3.52-3.36 (m, 4 H), 3.20-3.18 (br m, 4 H), 1.62-1.60 (br m, 4 H), 1.43-1.41 (br m, 2 H). MS (MALDI-TOF) *m/z* calcd for $M-H^+$ 1285.5, measured 1284.6. Anal. calcd for $C_{51}H_{88}N_6O_{39} \cdot 9H_2O$: C 38.98%, H 6.80%, N 5.35%. Found: C 38.83%, H, 6.68%, N 5.05%.
10. Integration values for **2** are approximate due to the broadness of some signals.