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Facile Synthesis of β-Cyclodextrin Dithiols

Jerry Yang* and David K. Leung

Department of Chemistry, Columbia University, New York, NY 10027, USA

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Abstract—Nucleophilic addition of 4-methoxy-α-toluenethiol to capped cyclodextrins followed by deprotection in TFA affords cyclodextrin dithiols in good yields with no disulfide formation and requires only minimal purification.

Cyclodextrins (CDs) are powerful tools in biomimetic chemistry. These readily available compounds are able to bind a wide variety of hydrophobic guests and are therefore very attractive as models for enzyme binding pockets.[1] Several methods have been developed for the selective functionalization of the free hydroxyl groups, most commonly employing the formation of sulfonate esters followed by subsequent manipulations to afford useful catalytic groups attached on either end of the CD hydrophobic cavity. Furthermore, CDs containing multiple functional groups have been synthesized and shown to be more successful as enzyme mimics than many monofunctionalized CDs.[2] Although the reactions that form these functionalized CDs are simplistic in design, they are often low yielding and in many cases produce complex reaction mixtures that are difficult to purify. In order to further explore the utility of CDs in biomimetic chemistry, it is important that new synthetic techniques be developed that incorporate these catalytic functional groups in useful quantities. Herein, we report a new facile method for synthesizing CDs containing free thiol groups. These thiols can be synthesized in relatively high yields in two steps from the known CD sulfonate esters with minimal purification.

Thiol groups are widely used in cyclodextrin chemistry due to their remarkable reactivity with electrophiles. In 1982, Fujita et al. reported a useful synthesis of 6-deoxy-6-mercapto-betacyclodextrin (β-CD-thiol).[3] This method entails the displacement of the primary tosylate ester located on the 6-position of one glucose residue with thiourea followed by basic hydrolysis to afford the free thiol. Tabushi also reported the synthesis of a β-CD-dithiol by using analogous methods on a capped cyclodextrin, however, the dithiol product required further chemical manipulation and purification to remove undesired disulfide contaminants.[4] Our own attempts at using this procedure to synthesize dithiols from the known AB (**1**), AC (**2**), and AD (**3**) capped β-CD's also resulted in complicated mixtures of products that were difficult to purify. We have since developed a new method for synthesizing these difunctionalized β-CDs in good yields.

The known capped β-CD disulfonate esters **1**–**3**[5] were stirred for 12 h at room temperature in an anhydrous DMF solution with 20 equivalent of 4-methoxy-α-toluene thiol and K_2CO_3 under argon to produce the corresponding bis-4-methoxy-α-toluene thioethers **1a**–**3a** in good yields after reverse-phase column chromatography[6] (Scheme 1). These bis-thioethers **1a**–**3a** were then dissolved in an anhydrous TFA solution containing 5% anisole and tentagel-SH beads.[7]

Previous work in our group demonstrated that modified CDs dissolved in anhydrous TFA can be recovered without destruction of the CD cavity. In a control experiment, β-CD was dissolved in TFA overnight, recovered by precipitation in ether, and shown to bind to *tert*-butylbenzoic acid with a binding constant of 1.5×10^4 M^{-1} by microcalorimetric titration, agreeing well with published values for similar binding groups[8] and indicating that the cyclodextrin was still intact.[9]

The reactions of **1a**–**3a** with TFA were allowed to stir under argon for 4 h after which the products were precipitated with diethyl ether, dissolved in mixtures of methanol and deionized water, filtered to remove the

*Corresponding author at present address: Harvard University, Department of Chemistry and Chemical Biology, 12 Oxford Street, Cambridge, MA 02138, USA. Tel.: +1-617-495-9434; fax: +1-617-495-2500. E-mail: jyang@gmwgroup.harvard.edu

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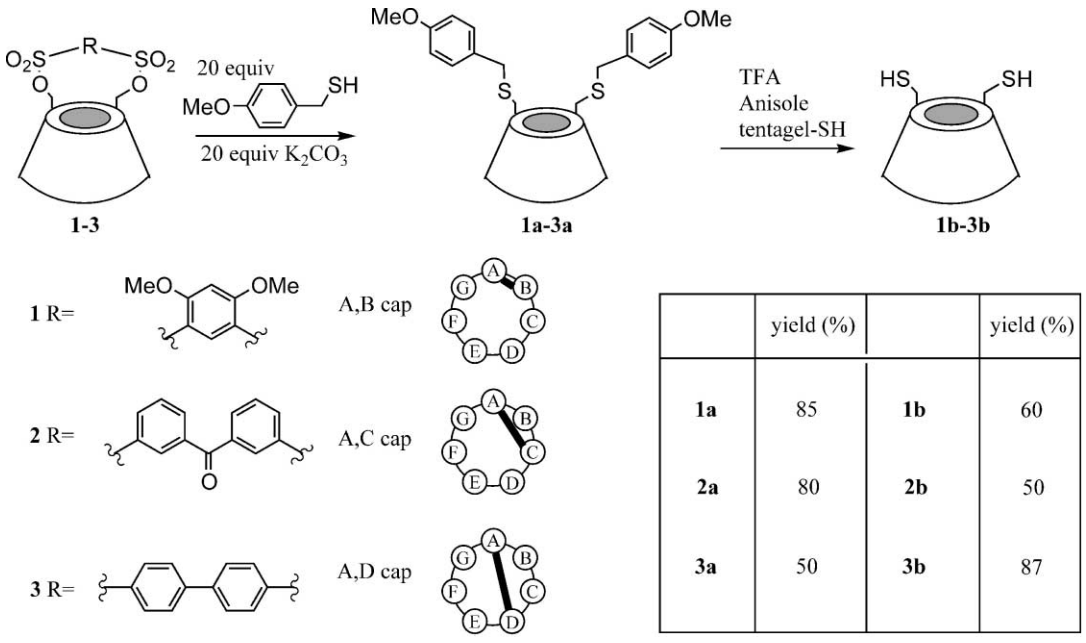

	yield (%)		yield (%)
1a	85	**1b**	60
2a	80	**2b**	50
3a	50	**3b**	87

Scheme 1.

tentagel beads, and dried to afford pure AB (**1b**), AC (**2b**), and AD (**3b**) dithiol products with no further purification in 50–87% yields from the corresponding bis-thioethers **1a**–**3a**.[10] All products were characterized by ^{1}H NMR, COSY, and MALDI-TOF mass spectroscopy.[11]

We have thus demonstrated a new simple method for synthesizing β-CD-dithiols. In this method, the final acidic deprotection to afford the free thiols appears to be less susceptible to oxidation to disulfides relative to conventional basic hydrolysis of thioureas or thioesters. An efficient synthesis of CD dithiols can provide an alternative method of synthesizing difunctionalized CDs, which usually consist of displacement of the corresponding CD diiodides with nucleophiles.

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6. Reverse-phase chromatography was performed using a gradient from 80:20 water/methanol to pure methanol, with products eluting at approximately a 50:50 water/methanol mixture.
7. The use of refluxing TFA or TFA/anisole with mercury acetate to cleave 4-methoxybenzyl thioethers has been reported earlier.[12] However, we found that TFA/anisole in the presence of a thiol at room temperature was sufficient for the deprotection step. Ten-fold excess by weight of the solid support beads were added to prevent disulfide formation. In the absence of the tentagel-SH, deprotection in TFA/anisole afforded mostly the bis-disulfide cyclodextrin dimers as characterized by ^{1}H NMR and MALDI mass spectroscopy [m/z 2369 ($M^+ + K^+$)]. The tentagel beads were used to facilitate the purification of the resulting cyclodextrin dithiols from the reaction mixture. Presumably, other thiols can be used to prevent disulfide formation during the deprotection step.
8. Breslow, R.; Halfon, S. *Proc. Natl. Acad. Sci. U.S.A* **1992**, *89*, 6916.
9. The ^{1}H NMR of β-cyclodextrin before and after dissolving in TFA was identical.
10. The remaining material was presumably lost during transfer or formed insoluble side products that were removed in the filtration step.
11. Compounds **1b**–**3b** had the same major peak by MALDI-TOF MS: m/z 1205 ($M^+ + K^+$). Compound **1b**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.50–6.60 (m, 14H), 4.75–4.90 (m, 7H), 4.10–4.70 (b, 5H), 2.60–4.00 (m, 32H expected; partially obstructed by HDO peak), 3.00–3.10 (m, 2H), 2.72–2.80 (m, 1H), 2.60–2.70 (m, 1H), 2.04–2.14 (m, 2H). Compound **2b**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.50–5.80 (m, 14H), 4.80–4.90 (m, 7H), 4.25–4.65 (b, 5H), 2.60–4.00 (m, 32H expected; partially obstructed by HDO peak), 2.90–3.00 (m, 2H), 2.70–2.80 (m, 1H), 2.60–2.70 (m, 1H), 2.00–2.10 (m, 2H). Compound **3b**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.50–6.00 (m, 14H), 4.78–4.90 (m, 7H), 4.15–4.70 (b, 5H), 2.60–4.00 (m, 32H expected; partially obstructed by HDO peak), 2.92–3.10 (m, 2H), 2.72–2.80 (m, 1H), 2.60–2.70 (m, 1H), 2.02–2.10 (m, 2H).
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