ChemPubSoc Europe

DOI: 10.1002/chem.201503131

CHEMISTRY A European Journal Full Paper

Host–Guest Systems

# Access to Versatile β-Cyclodextrin Scaffolds through Guest-Mediated Monoacylation

Nesrin Vurgun, Rodolfo F. Gómez-Biagi, and Mark Nitz*[a]

**Abstract:** Herein, we report the selective mono-derivatization of heptakis[6-deoxy-6-(2-aminoethylsulfanyl)]-β-CD (**1**) through a guest-mediated covalent capture strategy. The use of guests functionalized with cleavable linkers enables the installation of an amine-orthogonal thiol group on the primary rim of **1** as a handle for further transformations to the β-CD scaffold. Applying this methodology, two novel monoderivatized β-CDs were obtained in good yield and high purity. Both of these monoacylated CDs were amenable to facile linker cleavage and further modification at the resulting thiol group. This methodology can be applied towards the synthesis heterofunctionalized β-CD constructs for analyte sensing, drug delivery, and other applications.

## Introduction

β-CD is a naturally occurring cyclic oligomer comprised of seven 1,4-α-linked D-glucopyranosyl units.[1] The formation of β-CD host–guest complexes have been applied in a variety of areas including drug delivery, as components in commercial products and for enantiomeric separations.[1–7] While native β-CDs possess this innate property, their applications are limited due to their lack of functionality. In contrast, derivatized CDs feature a broader range of applications including catalysis,[1,8] polymer assembly,[9] molecular recognition of organic and biomacromolecules,[10–12] and targeted drug/DNA delivery.[2] While a multitude of applications exist for functionalized β-CDs, access to complex heterofunctionalized derivatives is currently hindered by the lack of efficient synthetic methods.

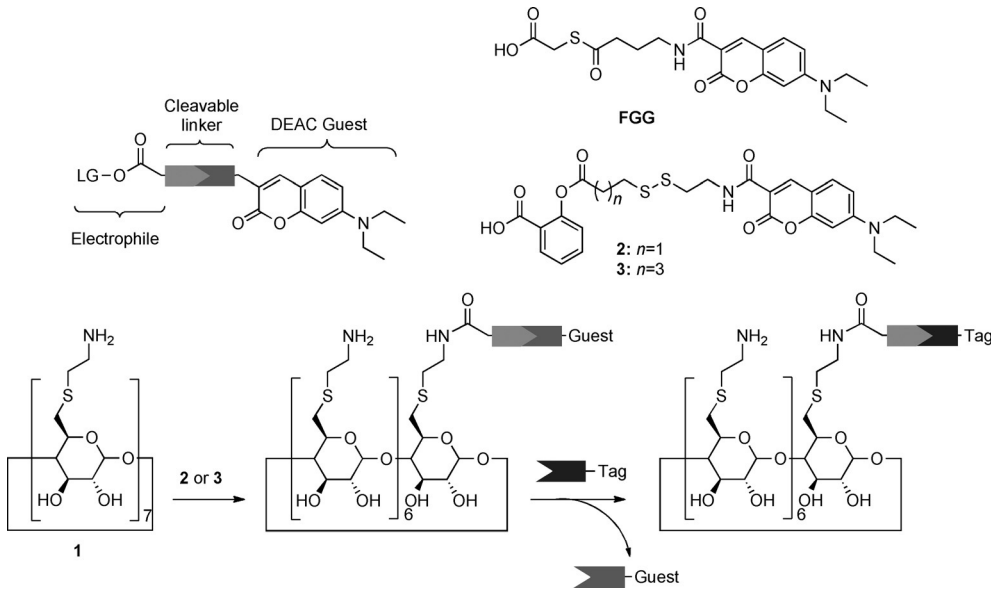
Derivatization of CDs may involve synthetic transformations of the primary or secondary glucoside hydroxyls.[1,13–16] CDs can be mono-, per-, or partially functionalized on the primary rim using appropriate reagents and protecting groups.[13,14] An impressive recent example has shown it is possible to orthogonally functionalize all six positions of α-CD.[17] Synthetic strategies that allow the selective modification of β-CD at the 2-, 3-, and 6- positions have also been reported.[18–23] Selective di- or trisubstitution requires capping strategies, such as the use of biphenyl-based disulfonates.[14,24] Other innovative methods to regioselectively functionalize CDs include selective diisobutylaluminium hydride (DIBAL-H)-promoted benzyl deprotection,[25–27] tandem azide reduction/deprotection,[28] tritylations,[29] and introduction of biselectrophiles.[30] Monoderivatization of the β-CD primary rim with a desired functional group often necessitates multiple synthetic steps. Usually, this is achieved by the monotosylation of a primary alcohol followed by nucleophilic displacement. Optimizing the monotosylation of CDs has been the subject of many studies.[14,31–33] However, selectivity remains a challenge and difficult chromatographic separations, and crystallizations, are required to remove side products. This monoderivatization methodology enables the introduction of a variety of substituents, such as a monoazide, amine, hydroxylamine, or thiol, which can then be further modified.[15,34,35] Amine-functionalized β-CD is a particularly desirable scaffold, which has been conjugated to a variety of biologically relevant molecules including glycodendrimers,[36,37] peptides,[38] proteins,[39] and drugs[2].

To complement existing methodologies and to address some of their inherent problems, we have developed a selective monoderivatization strategy based on the covalent capture of an activated guest by a nucleophilic β-CD. Covalent capture involves a supramolecular recognition event that accelerates the formation of a covalent bond between two reactive components in comparison to the bimolecular reaction.[40] If after reaction complex formation is prevented, significant selectivity for monofunctionalization can be achieved. Covalent capture with native CDs was initially demonstrated by Bender et al., who observed a significant rate acceleration for the acylation reaction of β-CD with *m*-nitrophenylacetate compared to the rate of background ester hydrolysis, and has since been successfully applied for CD-based catalysis.[41,42] This approach has also been used to monofunctionalize a calix[6]arene core, with various guests through a selective Huisgen cycloaddition reaction.[43,44]

Using covalent capture, we reported the selective monoderivatization of heptakis[6-deoxy-6-(2-aminoethylsulfanyl)]-β-CD (**1**).[45] Host–guest complexation between **1** and a thioester functionalized 7-diethylaminocoumarin-3-carboxylic acid (DEAC) guest (first-generation guest, **FFG**) facilitated S→N acyl

[a] *N. Vurgun, R. F. Gómez-Biagi, Prof. Dr. M. Nitz*
*Department of Chemistry, University of Toronto*
*80 St. George Street, Toronto, Ontario*
*M5S 3H6 (Canada)*
*E-mail: mnitz@chem.utoronto.ca*

*Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201503131.*




**Scheme 1.** Structure of DEAC-based guests, **2** and **3**, featuring cleavable linkers and the general scheme proposed to access desired heterofunctionalized CDs through the proposed methodology.

transfer with rate acceleration and high monoderivatization selectivity (Scheme 1).[45] The high selectivity of this reaction is the result of self-inclusion complex formation of the monoderivatized product, which prevents association of additional activated guests and limits further acylations. While this provided access to a high yield of monoderivatized **1**, the scope of the reaction was limited to direct covalent functionalization with a DEAC guest. We, therefore, sought to amend this strategy to increase the range of functional groups that could be incorporated.

Amine-functionalized CD **1** is a versatile scaffold, which has been used for the design of fluorescent sensors,[10,45] synthetic receptors,[46] investigated as a precursor to forming glycoclusters,[47] controlling protein self-assembly,[48] DNA transfection,[49] and as an inhibitor of anthrax lethal toxin.[50–53] In these examples, the amine groups of **1** were either per-functionalized, or monofunctionalized nonselectively with desired reagents. The installation of an amine-orthogonal functional group would augment the utility of **1**, by allowing for the synthesis of more complex heterofunctionalized derivatives. Furthermore, the higher affinity interactions of CD **1** with hydrophobic guests, compared to native β-CD, could be exploited to design more stable complexes.[54]

In this work, we describe a strategy to monofunctionalize **1** that enables access to heterofunctionalized CD scaffolds. Two activated disulfide-based linkers are investigated for monoderivatization of **1**, which after reduction and removal of the guest molecule reveal a thiol for further elaboration of the β-CD scaffold (Scheme 1).

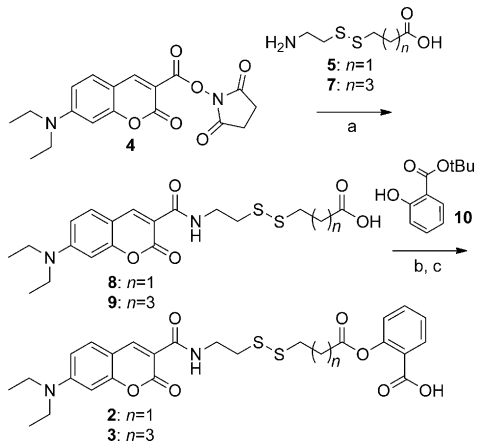
## Results and Discussion

### Design and synthesis of DEAC-based guests with cleavable linkers

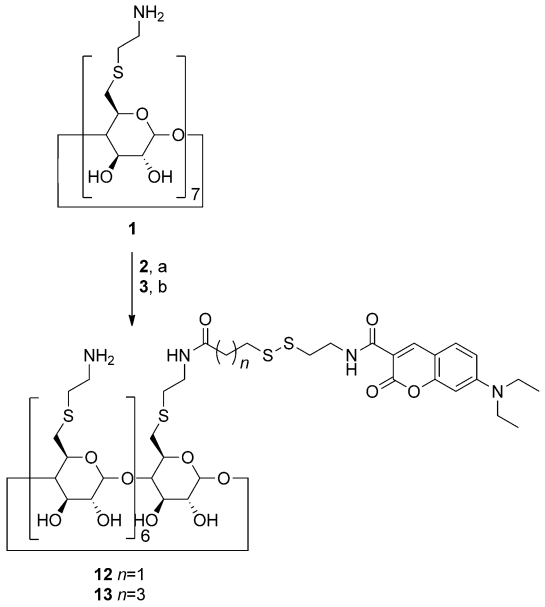
CD **1** forms a stable, high affinity host–guest complex with 7-diethylaminocoumarin-3-carboxylic acid (DEAC) ($K_a = 2.7 \times 10^6\ M^{-1}$, $NaHPO_4$ 0.05 M, pH 7.5).[54] To introduce a thiol on the primary rim of **1**, through a covalent capture strategy, two activated DEAC-based guests containing disulfide linkers, **2** and **3**, were synthesized (Scheme 1). Introduction of a thiol group to CD **1** was desired due to the compatibility of thiols with aqueous ligation chemistry and applications in bioconjugation.[55–57] Guests **2** and **3** contain alkyl linkers of differing length which will affect the rate of reaction with CD **1** and the propensity to form an intramolecular self-inclusion complex following monoderivatization.[45] The guests were activated as esters of salicylic acid to increase the guests' aqueous solubility and to provide favorable electrostatic interactions between the activated ester and the primary amines of **1**.

### Synthesis of guests 2 and 3

DEAC was synthesized as previously described and activated as a succinimide ester **4** (Scheme 2; see also the Supporting Information).[45] Linker **5**, was synthesized in 58% yield, in two steps. Cystamine hydrochloride was oxidized with *m*CPBA and the resulting sulfoxide was subsequently displaced with 3-mercaptopropionic acid. To prepare the longer linker, disulfide exchange between 5-mercaptopentanoic acid and 2,2′-dithiodipyridine was carried out, giving the activated disulfide **6** (74% yield). The resulting activated disulfide (**6**), was then exchanged with cysteamine hydrochloride, to afford linker **7** in 73% yield. Succinimide activated DEAC **4**, and linkers **5**, or **7**




**Scheme 2.** Synthesis of guests **2** and **3**: a) DIPEA, DMF, RT, o/n. 75% (**8**), 81% (**9**). b) DCC, DMAP, DCM, 0 °C→RT, 4 h, then TFA/DCM 4:1, RT, 6 h, 74% (**2**). c) DCC, DMAP, DCM, 0 °C→RT, o/n. 48%, then TFA/DCM 4:1, RT, 4 h, 41% (**3**). DCC = *N*,*N*-dicyclohexylcarbodiimide; DIPEA = *N*,*N*-diisopropylethylamine; DMAP = 4-dimethylaminopyridine.




**Scheme 3.** Synthesis of β-CD derivatives through guest-mediated monoacylation: a) **1** (1.0 equiv, 0.5 mM), **2** (1.0 equiv), borate buffer (0.1 M, pH 8.5), RT, 30 min 68%; b) **1** (1.0 equiv, 0.5 mM), **3** (1.0 equiv), borate buffer (0.1 M, pH 8.5), RT, 3 h, 63%.

were condensed overnight in the presence of DIPEA to yield compounds **8** and **9** in 75 and 81% yields, respectively. Compound **8** was activated as a salicylate ester by coupling with **10** and, following careful trifluoroacetic acid (TFA) deprotection, gave guest, **2** in 74% yield over two steps. Guest **3** was synthesized in an analogous manner. Protected intermediate **11** was synthesized in 48% yield from **9**. Intermediate **11** proved to be more stable than guest **3** for long-term storage. During TFA deprotection of **11**, a side product resulting from disulfide exchange was observed, accounting for the lower yield in this step, 41%, for guest **3**.

### Monoderivatization reactions

Reactions were optimized by controlling the equivalents of guest added, concentration of reagents in solution, and time of reaction. These factors were varied to assess the selectivity of reactions and to reduce reaction times. The reactions were monitored by MALDI-TOF MS to qualitatively monitor the reaction selectivity.

### Monoderivatization with disulfide guest 2

Reaction of **1** (0.5 mM) and guest **2** (1.0 equiv) in borate buffer (0.1 M, pH 8.5) gave the monoacylation product, **12**, in 30 min with a detectable amount of diacylated product (Scheme 3; see also the MALDI-TOF MS spectrum in the Supporting Information Figure S1). Guest **2** was readily solubilized upon addition to the reaction buffer in the presence of **1**. At higher concentrations, or if more than one equivalent of **2** was used in the reaction, the amount of over-acylated product formation increased. Purification by reverse-phase (RP)-HPLC was successful in removing over acylated products affording the desired monoderivatized product, **12**, in an isolated yield of 68%.

### Monoderivatization with disulfide guest 3

Reaction of **1** (0.5 mM) with guest **3** (1.0 equiv) in borate buffer (0.1 M, pH 8.5) was complete in 3 h (Scheme 3, see also the MALDI-TOF MS spectrum in Supporting Information Figure S2). The reaction proceeded with high selectivity and only the monoderivatized product, **13**, was observed by MALDI-TOF MS. Purification by (RP)-HPLC afforded the desired monoderivatized product, **13**, with a yield of 63%. We attribute the yield of this reaction to the reduced stability of the disulfide of guest **3** which may have decomposed during purification. It should also be noted that when reactant concentrations exceeded 2.0 mM, or equivalents of guest use were greater than 1.5 equivalents, the reaction selectivity decreased and diacylated product was observed. Below these thresholds, monoderivatized CD **13** could be obtained with exceptional selectivity.

### Kinetic analysis of monoderivatization reactions

To understand differences in the selectivity between the two monoderivatization reactions, and to determine the role of covalent capture in the reactions, the rates of both reactions were followed by UV/Vis spectroscopy. Ethylenediamine (EDA) was chosen to give a representative rate of aminolysis of guests in the absence of complex formation as the second $pK_a$ of EDA (7.63) is comparable to the least basic amine of **1** ($pK_a$ 7.37).[58] During these control experiments, EDA was used at an equivalent concentration to the amines of **1**. The release of the salicylate leaving group was monitored at 300 nm (Supporting Information, Figures S13 and S14). Upon acylation, the absorbance spectra of the coumarin did not change significantly.

In the presence of **1**, the rate of salicylate release is increased seven-fold for guest **2**, and eight-fold for guest **3** compared to the EDA control (Figure 1, see also the Supporting Information, Figures S15 and S16). Taking into account the EDA concentration, an effective concentration of 250 or 280 mM

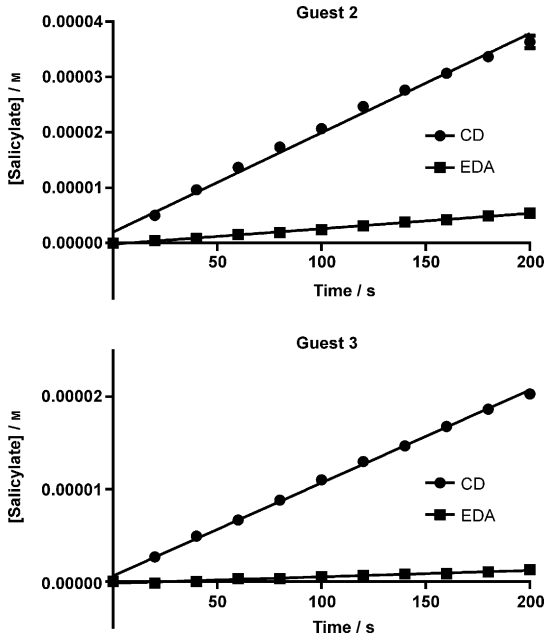



**Figure 1.** Salicylate release over time measured by UV/Vis (300 nm) for the aminolysis of guest **2** ($2.4\times10^{-4}$ M) or **3** ($2.4\times10^{-4}$ M) by CD **1** ($5.0\times10^{-3}$ M) or EDA ($3.75\times10^{-2}$ M) at 298 K, in borate buffer (0.1 M, pH 8.5).

can be calculated for the amines on CD **1**, for the reaction with guest **2** or **3**, respectively (see the Supporting Information p. 26). These values of effective concentration are also comparable to that observed in the reaction of CD **1** with guest **FGG** (230 mM). This suggests that guests **2** and **3** are as effective as **FGG** at facilitating the intramolecular amide bond formation reaction with **1**.[8,45,59]

In order to confirm that the rate accelerations observed are due to host–guest complexation, kinetic experiments were repeated in the presence of a competitive guest. These experiments were complicated by challenges of guest solubility. The rate of guest **2** aminolysis by CD **1** was 2.5-fold slower in the presence of 25-fold excess adamantane carboxylate (Supporting Information, Figure S17). Unfortunately, under the same conditions, the rate of reaction could not be measured for guest **3**, due to unexpected changes in the absorbance spectrum likely due to aggregate formation (Supporting Information, Figure S18). Additional experiments under more dilute conditions with bicine buffer (0.1 M, pH 8.5) showed the rate of aminolysis of guest **2** by CD **1** was approximately two times slower in the presence of a 10-fold excess of adamantane carboxylic acid or coumarin **8** (Figure 2; see also the Supporting Information Figures S19 and S20). Similarly, for guest **3**, the rate of aminolysis was reduced by two- or five-fold in the presence of adamantane carboxylate or coumarin **9**, respectively (Figure 2; see also the Supporting Information Figure S22). The

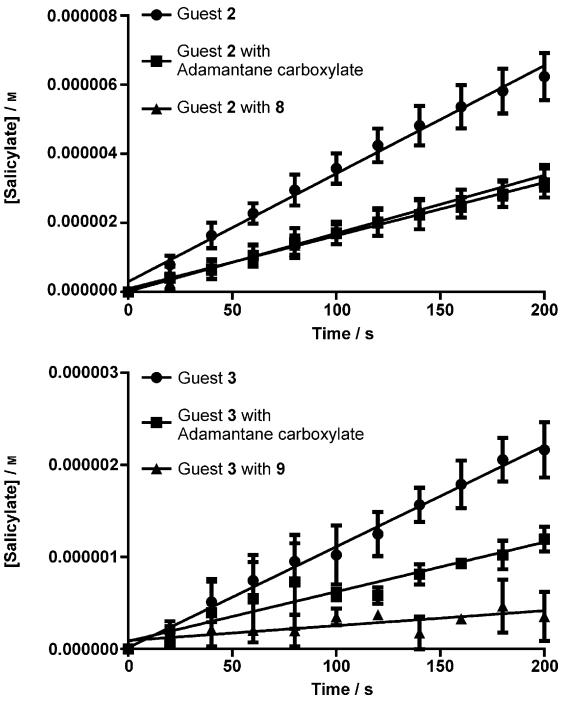



**Figure 2.** Salicylate release over time measured by UV/Vis (300 nm) for the aminolysis of guest **2** ($2.0\times10^{-5}$ M) or **3** ($2.0\times10^{-5}$ M) by CD **1** ($2.0\times10^{-4}$ M) at 298 K in bicine buffer (0.1 M, pH 8.5). Reactions were performed in the presence or absence of competitive guest, adamantanecarboxylic acid ($2.0\times10^{-4}$ M), or coumarin **8** or **9** ($2.0\times10^{-4}$ M) binding.

decreases in the observed rates are consistent with the extent of competitive complex formation expected under the experimental conditions and are consistent with a covalent capture mechanism.

## ROESY- and DOSY-NMR studies of monoderivatized products

ROESY-NMR spectra of **12** and **13** were collected to detect the presence of self-inclusion complexes. ROE cross-peaks between the $^1$H resonances of the DEAC guest and the H-3s and H-5s of the β-CD are diagnostic of inclusion complex formation. These characteristic ROE cross-peaks were not observed for compound **12** (Figure 3; see also the Supporting Information Figures S23 and S24 and Table S1). This suggests that self-inclusion of the covalently bound guest is not favorable. This observation may explain the multiply acylated products observed in the monoderivatization reactions with guest **2**; after monoacylation, the covalently bound guest does not reside in the cavity, allowing the binding of other activated guests and subsequent acylations.

In contrast, ROE-cross-peaks between DEAC aromatic protons H-C and H-D and DEAC methyl protons, H-F, with the H-3 and H-5 protons of the CD are observed for compound **13** (Figure 3; see also the Supporting Information Figures S25 and S26 and Table S2). Previously, similar ROE cross-peaks for the reaction product of our first-generation guest **FGG** and **1** were observed.[45] To rule out the possibility of intermolecular daisy-chain formation, DOSY-NMR[60–61] was also carried out for CDs

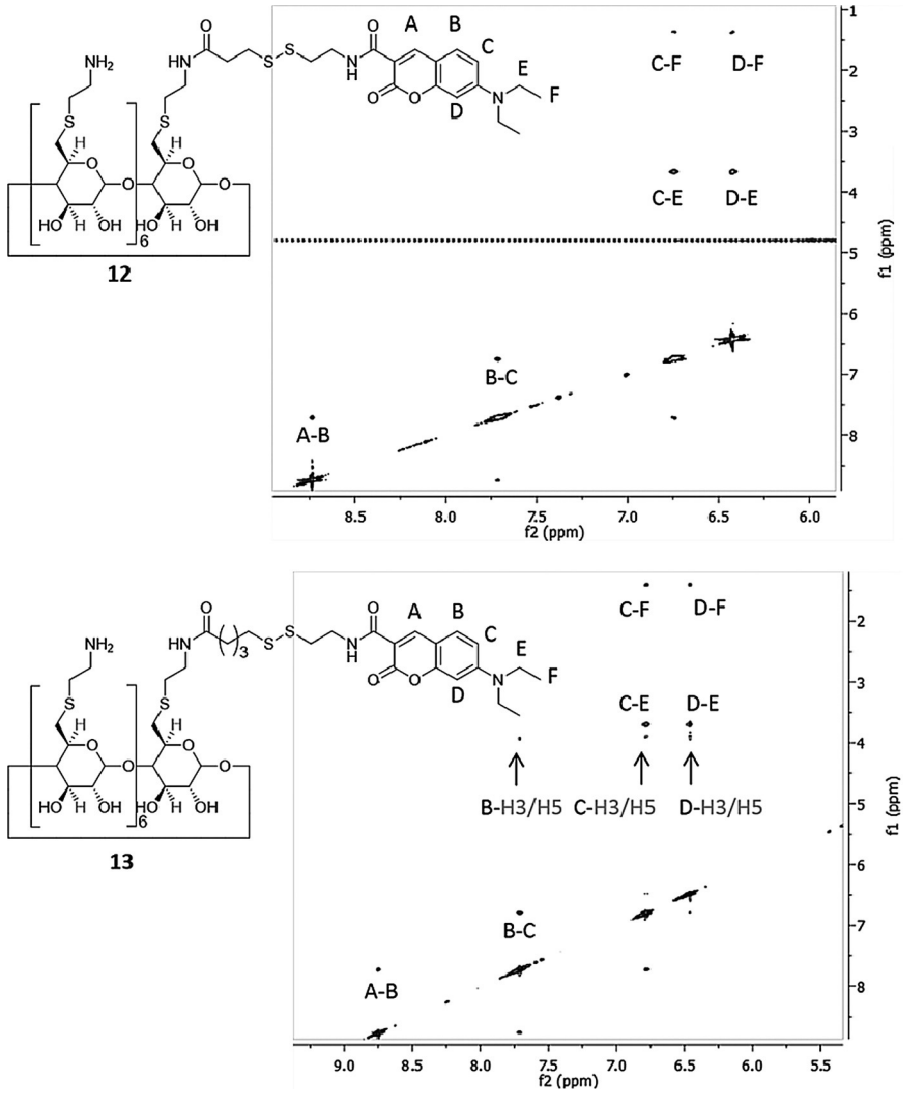



**Figure 3.** ROESY cross-peaks observed between the CD H-3 and H-5 protons and coumarin guest protons for CDs **12** (top) and **13** (bottom).

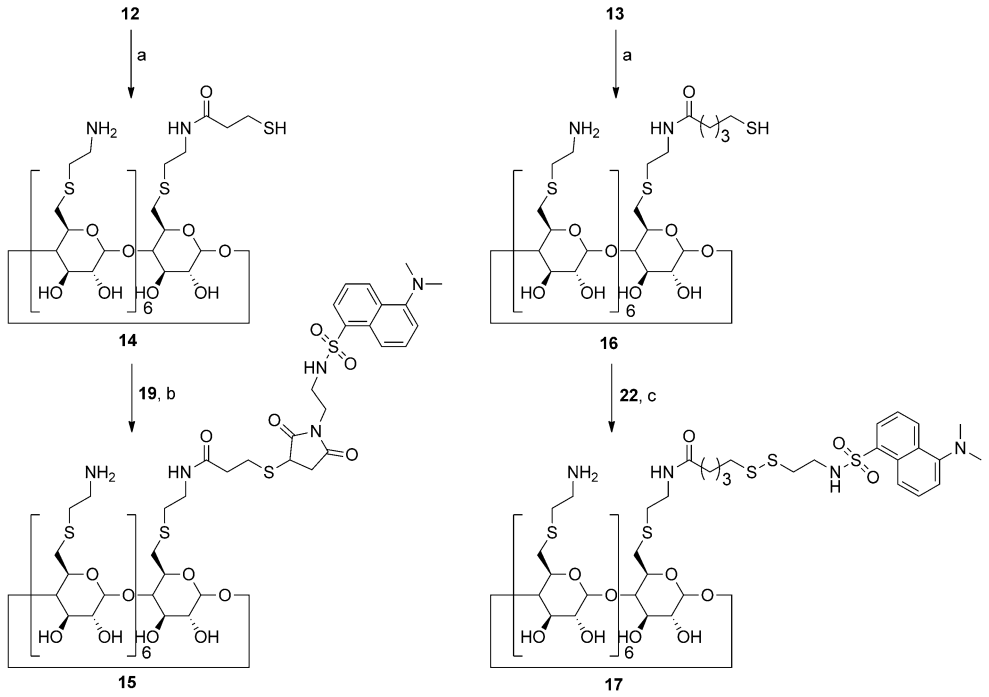
**12** and **13** (10 mM, $D_2O$, Supporting Information Figures S27–S31). As the monomeric controls, inclusion complexes of coumarin **8** or **9** with CD **1** were prepared. The diffusion coefficients measured for the four coumarin ring protons in the monoderivatized species were identical to those of the monomeric controls, which suggests that CDs **12** and **13** exist as monomeric species in solution. These data support CD **13** adopting a self-inclusion complex and which disfavors multiple acylation reactions during the functionalization reaction.

The suboptimal linker length of **2** or the geometry of the disulfide bond may be factors which destabilize the self-included complex in **12**. While this does limit the inherent selectivity of the reaction between **2** and **1** at high reagent concentrations, the formation of multiply acylated products is successfully curbed by using stoichiometric amounts of activated guest under high dilution conditions. This issue is mitigated with the longer linker design in guest **3** which allows covalently bound guest **13** to adopt a favorable self-included conformation, enabling monoacylation of **1** with exquisite selectivity.

### Linker cleavage and further derivatization

To assess the feasibility of further functionalization of **12** and **13**, maleimide chemistry and disulfide exchange with dansyl-modified reagents were investigated after reduction with excess aqueous tris(2-carboxyethyl)phosphine (TCEP) (100 equiv) (Scheme 4). The desired thiols **14** and **16** were purified by cation-exchange chromatography (CM Sephadex C-25). To facilitate the removal of the reduced coumarin guest, the resin was washed with additional aqueous TCEP solution and MeOH. The reduced CD was then eluted with 5% $NH_4OH$. CDs **14** and **16** were stored under vacuum at RT to prevent oxidation.

Dansyl-functionalized maleimide **19** in DMSO was added to a solution of CD **14** in water/acetic acid (pH 4.5), and incubated for 4 h. The desired CD construct **15** was purified by HPLC and characterized by ESI-MS, and $^1H$ NMR (Supporting Information Figures S9 and S10). It should be noted that side products were formed through the reaction of CD **1** amines with malei-




**Scheme 4.** Linker cleavage and functionalization at the resulting thiol for CDs **12** and **13**: a) Buffered TCEP (100 equiv) solution, RT, 20 min, 95% (**14**), 93% (**13**); b) **19** (1.0 equiv), AcOH, DMSO/$H_2O$, RT, 4 h, 29%; c) **22** (1.0 equiv), AcOH, DMSO/$H_2O$, RT, 4 h, 47%.

mide **19**, and these could be successfully removed during purification. The unexpected CD **1** amine reactivity may be attributed to their depressed p$K_a$. Incubation with sub-stoichiometric **19** at 0 °C was found to reduce side-product formation.

Functionalization of the CD thiol through disulfide exchange was investigated to increase the selectivity of the derivatization. Dansyl **22**, containing a pyridine-2-thiol leaving group, in DMSO, was added to a solution of CD **16** in water/acetic acid (pH 5), and incubated for 4 h. The desired CD construct **17** was purified by HPLC and characterized by ESI-MS and $^1$H NMR (Supporting Information Figures S11 and S12). As expected, no side reactions were observed and the desired construct **17** could be isolated in good yields.

These reactions demonstrate that the envisioned linker cleavage strategy is a feasible method for further functionalizing the CD **1** scaffold, and may enable its conjugation to a range of desired groups such as biomolecules.

## Conclusion

In summary, guest-mediated monoacylation is an effective strategy to install an orthogonal functional group on the primary rim of **1**, with high selectivity, good yields, and short reaction times. Aminolysis of guests **2** and **3** by **1** proceeds with rate acceleration due to host–guest complexation, and demonstrates a key principle of covalent capture. The high guest affinity of CD **1** allows for these conjugation reactions to proceed rapidly even under dilute conditions (low μM). Upon linker cleavage, CDs **12** and **13** can be functionalized with a variety of compatible compounds at the resulting thiol. In addition, the complex structures may be readily modified on the remaining primary amines. CDs **12** and **13** can, therefore, serve as versatile scaffolds for the synthesis of heterofunctionalized β-CDs to combine molecular sensing, targeted drug delivery or catalysis capabilities with multivalent presentation of recognition sites for biomolecules. The general synthetic strategy described here could, furthermore, be adapted to facilitate the derivatization of other CDs by modifying the size of the included guest, or enable generation of other scaffolds through the use of different cleavable linker designs.

## Experimental Section

### General information

All chemicals or reagents were purchased from Sigma Aldrich or Alfa Aesar. Dry solvents were purchased from Acros chemicals. All reactions were performed under a nitrogen-atmosphere and at room temperature, unless stated otherwise. $^1$H- and $^{13}$C NMR spectra were recorded on a Varian 400 MHz, Agilent DD500 MHz, or Bruker 400 MHz spectrometers at $T = 297$ K. 1D $^1$H NMR and 2D ROESY studies of monoderivatized CDs were recorded on an Agilent DD700 MHz spectrometer. DOSY studies of CD inclusion complexes and monoderivatized CDs were recorded on a Varian 500 MHz spectrometer. Absorption spectra and kinetics experiments were measured on a Shimadzu UV-2401PC spectrophotometer at $T = 298$ K. Semi-preparative HPLC separations were performed on a Waters 1525 Binary HPLC pump and Waters 2487 dual $\lambda$ absorption detector using a Waters XBridgeTM Prep BEH130 C18 5 μm (10×250 mm) reverse-phase column. Analytical HPLC separations were performed on a Perkin–Elmer Series 200 pump and Waters 2487 dual $\lambda$ absorption detector using an Agilent Zorbax RX-C18 5 μm (4.6×250 mm) reverse-phase column. High resolution mass spectra were obtained from an ABI/Sciex QStar mass spec-

trometer with an ESI source. The MALDI spectra were taken using a Waters Micromass MALDI micro MX™ (matrix-assisted laser/desorption/ionization time-of-flight mass spectrometer [MALDI-ToF MS]) using α-cyano-4-hydroxycinnamic acid matrix. For the synthesis of guests **2** and **3**, and other CD derivatives, as well as analytical data please refer to the Supporting Information.

### Heptakis-[6-deoxy-6-(2-aminoethylsulfanyl)]-β-CD (1)

CD **1** was prepared according to a literature procedure.[54] $^1$H NMR (400 MHz, $D_2O$): $\delta = 5.16$ (d, $J = 3.70$ Hz, 7H), 4.06 (ddd, $J = 9.5$, 6.5, 2.6 Hz, 6H), 3.96 (m, 7H), 3.68 (m, 14H), 3.30 (t, $J = 6.7$ Hz, 14H), 3.18 (dd, $J = 14.6$, 2.6 Hz, 6H), 3.05 (m, 7H), 3.02 ppm (t, $J = 6.7$ Hz, 14H).

### Monoderivatization with activated guest 2

CD **1** (32.3 mg, 0.018 mmol was dissolved in borate buffer (42.0 mL, 0.1 M, pH 8.5) to give a final concentration of 0.5 mM. Disulfide guest **2** (8.9 mg, 0.018 mmol) was added, and the resulting solution was vigorously stirred at RT for 30 min. The solution was then lyophilized and the resulting solid was purified by reverse-phase HPLC, to yield CD **12** a fluffy yellow solid. Isolated yield: 68%; $[\alpha]_D^{20} = +104.36^\circ$ ($c = 0.5$ in $H_2O$); $^1$H NMR (700 MHz, $D_2O$): $\delta =$ 8.74 (1H, s), 7.71 (d, $J = 8.9$ Hz, 1H), 6.75 (d, $J = 9.0$ Hz, 1H), 6.42 (s, 1H), 5.12 (m, 7H), 3.79 (m, 41H), 3.44 (m, 4H), 3.27 (m, 58H), 1.37 ppm (t, $J = 6.5$ Hz, 6H); HRMS-ESI: *m/z*: calcd for $C_{75}H_{130}N_9O_{32}S_9$: 652.2166 $[M+3H]^{3+}$; found: 652.2097.

### Monoderivatization with activated guest 3

CD **1** (74.8 mg, 0.048 mmol) was dissolved in borate buffer (100 mL, 0.1 M, pH 8.5) to a final concentration of 0.5 mM. Disulfide guest **3** (27.7 mg, 0.048 mmol) was added, and the resulting solution was vigorously stirred at RT for 3 h. The solution was then lyophilized and the resulting solid was purified by reverse-phase HPLC to yield CD **13** as a fluffy yellow solid. Isolated yield: 63%; $[\alpha]_D^{20} = +83.17^\circ$ ($c = 0.5$ in $H_2O$); $^1$H NMR (700 MHz, $D_2O$): $\delta = 7.44$–7.30 (m, 1H), 6.44–6.41 (m, 1H), 5.07–4.48 (m, 5H), 3.60–3.43 (m, 7H), 3.43–3.04 (m, 22H), 3.02–2.84 (m, 17H), 2.84–2.78 (m, 3H), 2.78–2.44 (m, 25H), 2.40–2.31 (m, 2H), 8.43–8.34 (m, 1H), 1.96 (t, $J = 6.6$ Hz, 3H), 1.12 (p, $J = 7.4$ Hz, 3H), 6.12–6.09 (m, 1H), 1.50–1.23 (m, 5H), 1.03 ppm (t, $J = 7.2$ Hz, 10H); HRMS-ESI: *m/z*: calcd for $C_{77}H_{134}N_9O_{32}S_9$: 661.5543 $[M+3H]^{3+}$; found: 661.5544.

## Acknowledgements

The authors kindly acknowledge the Natural Science and Engineering Research Council of Canada (NSERC) for funding this work. We would also like to thank Dr. D. Burns and D. Pichugin for their help with NMR experiments.

**Keywords:** covalent capture · cyclodextrin · host–guest systems · selective functionalization

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Received: August 8, 2015
Published online on December 4, 2015