Synthesis and Reactivity of 6-β-Cyclodextrin Monoaldehyde: An Electrophilic Cyclodextrin for the Derivatization of Macromolecules under Mild Conditions

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Introduction

Currently, there is increasing interest in reactive cyclodextrins for applications in the areas of materials science, molecular devices, chromatographic supports, and as drug delivery vehicles.[1-5] Although a number of reactive cyclodextrins[6] are commonly used in constructing new materials for such applications, cyclodextrin tosylate has been the most commonly employed reactive cyclodextrin intermediate. For example, cyclodextrin tosylate has been recently utilized for the attachment of β-cyclodextrin to polyamines in DMSO in the preparation water soluble catalytic polymers.[7] However, the cyclodextrin tosylate route generally requires the use of anhydrous organic solvents and elevated temperatures to effect alkylation. Such conditions are incompatible with most bioconjugation applications because proteins and many other biomolecules will generally not tolerate such conditions.

Cyclodextrin aldehyde, on the other hand, is perhaps the most appropriate reactive cyclodextrin candidate for attachment to biomolecules. Unlike cyclodextrin tosylates and halides,[8] cyclodextrin aldehyde is highly water soluble and can be efficiently reacted with proteins or other water soluble polymers under the facile conditions of Schiff base or hydrazone formation and subsequent reduction.[9] By using 6-β-cyclodextrin aldehyde **3** for the derivatization of biomolecules, the need for organic solvents, excessive heating or prior protein modification are eliminated. Current methods[10,11] for the synthesis of 6-β-cyclodextrin monoaldehyde, however, require as many as four steps and necessitate the use of toxic and potentially explosive azides.[12]

We have developed a facile synthetic route for the conversion of β-cyclodextrin **1** to 6-β-cyclodextrin monoaldehyde **3** (Scheme 1). Our method utilizes the readily available monotosylate **2** as the key synthetic intermediate,[13,14] but does not require the synthesis of an azide or amine in order to obtain the final product **3** as in previously reported syntheses of **3**.[10,11]

Results

Our route to 6-β-cylodextrin aldehyde is a simple two-step procedure requiring the conversion of β-cyclodextrin to its monotosylate[13,14] followed by a DMSO-mediated oxidation using 0.2–0.3 equiv of Hunig's base (diisopropylethylamine) as a catalyst (Scheme 1). Other hindered amine bases, as well as trace amounts of sodium hydroxide, also facilitated this reaction. Under acidic conditions in DMSO, no appearance of aldehyde **3** from **2** was observed.[15] When the oxidation was attempted in DMF in the absence of DMSO, no oxidation of **2** to **3** was observed. Initial attempts to oxidize the 6-β-cyclodextrin monotosylate with trimethylamine *N*-oxide or *N*-methylmorpholine *N*-oxide in DMSO led exclusively to a product **4** resulting from β-elimination (Scheme 1). The conversion of **2** to **4** using amine *N*-oxides was also effected using DMF as a solvent. Thus, the oxidation of **2** to **4** in the presence of *N*-oxides occurs without any participation of DMSO in the mechanism. We also discuss here the synthesis and characterization of the bifunctional cleavage product of β-cyclodextrins.

Synthesis of Cyclodextrin Aldhehyde 3. We found that heating β-cyclodextrin monotosylate to 80 °C in DMSO, in the absence of amine base, resulted in the slow conversion of the tosylate to the aliphatic 6-β-cyclodextrin aldehyde **3.** This conversion took up to 1.5 weeks for completion at 80 °C. The aliphatic monoaldehyde **3** had a ^{1}H NMR resonance at δ 9.7 and a ^{13}C NMR resonance at δ 198.2.

The addition of 0.2–0.3 equiv of diisopropylethylamine considerably accelerated the conversion of the tosylate to the aldehyde. This enabled acceptable yields of 6-β-cyclodextrin monoaldehyde **3** to be obtained via this procedure within 2 days at 80 °C. Several other bases, including diisopropylamine, *N*-methylmorpholine, triethylamine, trimethylamine, 1,8-bis(dimethylamino)-naphthalene (Proton Sponge), or trace amounts of NaOH (Table 2) were investigated as catalysts for this conversion.

Although the 6-β-cyclodextrin monotosylate (**2**) was completely consumed after heating in DMSO to 80 °C for 3 days in the presence of catalytic base, only partial apparent conversion to the aldehyde **3** was observed under these conditions while monitoring the reaction by ^{1}H NMR in d_6-DMSO. We also noted that the formyl proton peak of the aldehyde at δ 9.7 for **3** disappeared completely from the ^{1}H NMR spectrum upon the addition of D_2O to the crude reaction mixture in d_6-DMSO. This is presumably the result of hydrate formation causing the resonance for this proton to become buried in a broad peak in the 4.5–5 ppm range corresponding to the anomeric region of the cyclodextrin spectrum in d_6-DMSO. After precipitation of the monoaldehyde **3** and exposure to high vacuum overnight, no carbonyl peaks were observed in the IR spectrum of isolate **3**. Apparently, autoxidation of the aldehyde to the carboxylic acid does not occur.[16]

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Scheme 1. Conversion of β-Cyclodextrin to Its Monoaldehyde 3 and the β-Eliminated Derivative 4

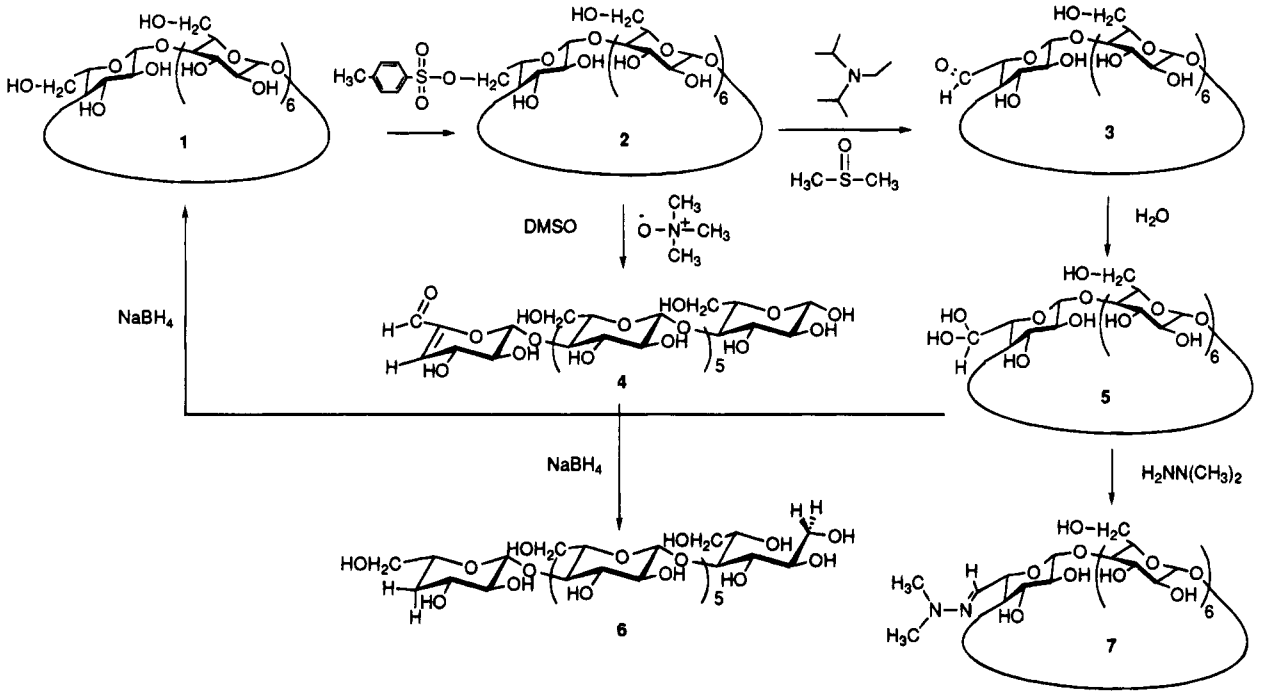

Table 1. Mass Spectral Characterization Data for Various β-Cyclodextrin Aldehyde Derivatives Using ESI-MS and PDMS Techniques

compd	description	molec formula	technique	molec ion calcd	molec ion obsd
1	β-cyclodextrin starting material	$C_{42}H_{70}O_{35}$	ESI	1136.0	1136.2
3	6-β-CD monoaldehyde	$C_{42}H_{68}O_{35}$	ESI	1134.0	1133.9
1	$NaBH_4$ reduction product of **3**	$C_{42}H_{70}O_{35}$	ESI	1136.0	1137.3
7	*N,N*-dimethylhydrazone derivative of **3**	$C_{44}H_{74}N_2O_{34}$	(+) PDMS (BIOION)	1176.1	1177.1
4	β-elimination product	$C_{42}H_{68}O_{35}$	ESI	1134.0	1135.0
6	$NaBH_4$ reduction product of **4**	$C_{42}H_{74}O_{35}$	ESI	1140.0	1140.0

Table 2. Conditions for Oxidation of 6-β-Cyclodextrin Tosylate 2 to Aldehyde 3 or 4 in DMSO at 80 °C

entry	reagents	condns	product
1	*N*-methylmorpholine *N*-oxide	1.0 equiv of *N*-oxide	**4**
2	*N*-methylmorpholine	1.0 equiv NMM	**3**
3	*N*-methylmorpholine	10.0 equiv NMM	**4**
4	trimethylamine *N*-oxide	1.0 equiv	**4**
5	trimethylamine	saturated soln	**4**
6	diisopropylethylamine	0.3 equiv	**3**
7	triethylamine	0.3 equiv	**3**
8	1,8-bis(dimethylamino) naphthalene	0.3 equiv	**3**
9	sodium hydroxide	trace[a]	**3**

[a] We noted that β-cyclodextrin tosylate **2** prepared by the method of ref 14 when used without further purification was converted to aldehyde **3** in DMSO more rapidly than was HPLC purified **2**. Measurement of the pH of an aqueous solution of HPLC-purified tosylate and non-HPLC purified tosylate produced by this procedure revealed that the non-HPLC purified material was about 100−1000 times more basic than the purified material.

These observations are consistent with the known formation of the hydrate **5** or hemiacetal (Scheme 1) from aldehydes.

Synthesis of β-Elimination Product 4. Our initial attempts to synthesize 6-β-cyclodextrin monoaldehyde **2** utilized a reaction in which the the tosylate of **2** was displaced by trimethylamine *N*-oxide with subsequent elimination of trimethylamine to form the aldehyde. Recently, Ganem et al.[17] reported that yields of trimethylamine *N*-oxide mediated oxidations of aliphatic bromides could be increased by heating alkyl halides in DMSO as compared to the usually employed conditions of refluxing $CHCl_3$.[18] However, after 6-β-cyclodextrin monotosylate[13,14] (**2**) was heated for several hours in DMSO at 80 °C in the presence of 7.0 equiv of anhydrous[19] trimethylamine *N*-oxide (TMANO), the α,β unsaturated aldehyde product **4**, with a formyl ^1H NMR resonance at δ 9.3 and a ^{13}C NMR resonance at δ 187.4, was the only product observed by NMR. The β-elimination product **4** was also observed by NMR using *N*-methylmorpholine *N*-oxide (NMMNO) as the oxidizing agent under similar conditions.

We also found that the use of 1.0 equiv *N*-methylmorpholine *N*-oxide as an oxidant in DMSO with tosylate **2** resulted in predominantly β-elimination product **4**. However, the presence of 1.0 equiv of *N*-methylmorpholine during the oxidation of tosylate in DMSO did not induce β-elimination (Table 2). Thus, the 1.0 equiv of free base released during the *N*-oxide-mediated oxidation is apparently not in itself sufficient to induce β-elimination. However, significant β-elimination was observed in cases where the excess of base (e.g., *N*-methyl morpholine) to monotosylate **2** was around 10.0 equiv or when a saturated solution of trimethylamine in DMSO was heated to 80 °C in the presence of monotosylate **2**.

Characterization of 3 and 4. Isolation of 6-β-cyclodextrin monoaldehyde (**3**) was accomplished by

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precipitation of the product from the reaction mixture upon the addition of acetone. Crude yields of up to 92% were obtained using this procedure, although the solid 6-β-cyclodextrin product was typically isolated as the hydrate **5** with yields around 85% (Scheme 1) after precipitation. Pure cyclodextrin aldehyde was difficult to isolate directly by precipitation or HPLC, presumably due to complexation of **3** with the *p*-toluenesulfonic acid reaction byproduct. However, the 1,1-dimethylhydrazone derivative **7** (Scheme 1) was prepared and readily crystallized from methanol. The ^{1}H NMR spectrum of compound **7** yield doublets (J = 5.4 Hz) for the formyl proton of the syn and anti hydrazones at δ 6.35 and 6.57 respectively. The mass spectral data for **7** are presented in Table 1.

Unlike the 6-β-cyclodextrin monoaldehyde **3**, the α,β-unsaturated aldehyde **4** does not form the hydrate as readily as **3** and the aldehyde peak at δ 9.3 remains visible in the ^{1}H NMR even after the addition of D_2O.

The structures of 6-β-cyclodextrin monoaldehyde **3** and β-elimination product **4** were also supported by mass spectral data. The various derivatives of **3** and **4** used for the characterization of these compounds are shown in Scheme 1. Mass spectral data using EI and FAB techniques were ambiguous, but plasma desorbtion mass spectrometry, or (+) PDMS (BIOION), spectra revealed support for the structures **3** and **4**.[20] Mass spectral data for the characterization of **3** and **4** were also obtained using ESI (electrospray) MS technique or reversed phase HPLC ESI MS.[21] The determination of molecular ions by ESI for β-cyclodextrin **1** (calcd 1136.0, obsd 1136.2) is compared to mono aldehyde **3** (calcd 1134.0, obsd 1133.9) and β-elimination product **4** (calcd 1134.0, obsd 1135.5). ESI MS data for the hydrazone derivative **7** (Scheme 1) shows an observed mass of 1177.4 with a calculated mass of 1176.1 for $C_{44}H_{74}N_2O_{34}$ (Table 1). Plasma desorbtion data for **7** were also obtained and are included in Table 1. The ESI mass spectra of β-cyclodextrin **1**, monoaldehyde **3**, and hydrazone derivative **7** are shown in Figure 1.

As additional confirmation of the 6-β-cyclodextrin monoaldehyde structure, the reduction of **3** with $NaBH_4$ was performed. The reduction of **3** leads to a compound identical in mass spectral data, within experimental error, to cyclodextrin **1**. The ^{1}H NMR spectrum of product obtained by the reduction of **3** is also indistinguishable from that for **1**. Electrospray mass spectrometry, or ESIMS, data for reduction product of **3** are found in Table 1. The reduction of **4** (Scheme 1) leads to product **6**. Compound **6** is the result of a 1,4 and 1,2 reduction of the α,β-unsaturated aldehyde portion of **4**, as well as the reduction of the anomeric hemiacetal of **4**. The calculated (1140.0) and observed (1140.0) mass of **6**, as obtained by ESI MS, is included in Table 1.

We also conducted TLC experiments[11] in support of structure **3**. We found that the reduction product derived from $NaBH_4$ reduction of **3** had TLC properties identical to β-cyclodextrin **1**. The R_f value for the product of the reaction of **3** with $NaBH_4$ was 0.4, identical to that of β-cyclodextrin **1**, on silica gel using a 1:1 ratio of a 10:8:3 *n*-butanol/ethanol/water solution and a 12:3:4 butanone/methanol/acetic acid solution.

A resonance for the aliphatic 6-β-cyclodextrin monoaldehyde **3** of β-cyclodextrin at δ 198 ppm is observed in ^{13}C NMR. For the β-elimination product **4**, the aldehyde peak is observed at δ 187.2 ppm and the two olefinic resonances are observed at δ 124.2 and 147.8 ppm for the 4′-β and 5′ α-carbons, respectively.

Discussion

Unlike many commonly employed DMSO-mediated oxidations,[22-24] this method enables the conversion of β-cyclodextrin **1** to its monoaldehyde **3** without requiring activation of the DMSO with an electrophophile (e.g., DCC, tosyl chloride).[25,26] Also, the problem of multiple oxidations possible with one-step direct oxidations of **1** to **3** is avoided by the synthesis and isolation of the the monotosylate **2** to effect the specific oxidation of the tosylate to the aldehyde. The remaining hydroxyl groups on the 6-β-cyclodextrin monotosylate **2** need not be protected using our route. This affords a significant advantage over alternative direct oxidation procedures such as the Binkley[27] oxidation, ferrate oxidation,[28] or chromium trioxide[29] based oxidations.

The nucleophilicity of DMSO is apparently sufficient to displace the tosylate on **2** under the conditions used for this conversion. After formation of the sulfonium intermediate by the reaction of DMSO with tosylate **2**, loss of the α proton with simultaneous displacement of dimethyl sulfide presumably ensues by the usual mechanism.[24] The rate of this reaction can be accelerated by the addition of a catalytic amount of a hindered amine base, presumably because of the base-catalyzed formation of nucleophilic DMSO anion. The abstraction of the α proton of the resultant 6-β-cyclodextrin aldehyde **3** by a catalytic base, leading to β-elimination, is apparently disfavored by using a non-nucleophilic hindered base.

In the presence of amine *N*-oxides, a different mechanism apparently dominates and the β-elimination product **4** is observed. Our attempts at the oxidation of **2** to **3** via *N*-oxide chemistry led to the α,β unsaturated product **4**. Similar β-elimination products were also observed by Horton et al.[30] in attempting the oxidation of the 6-hydroxyl on amyloses under basic conditions. Conditions for inducing β-elimination in carbohydrate oligomers are well precedented,[30-32] but to our knowledge, this is the first example of an amine *N*-oxide induced β-elimination from the 6-tosyl esters of cyclodextrins.

(20) The molecular ion for 6-β-cyclodextrin monoaldehyde **3** was observed for $C_{42}H_{68}O_{35}$ at 1155.5 (calcd 1155.9) for M^+ (Na^+) using plasma desorption mass spectrometry. With the β-elimination product **4**, a molecular ion was also observed at 1156.2 (calcd 1155.9) for M^+ (+ Na^+) for $C_{42}O_{68}O_{35}$ using the PDMS technique. Although the molecular formulas for the two aldehydes **3** and **4** are identical, a loss of 142.7 mass units from β-elimination product **4**, yielding a major peak at 1014.5, is observed by PDMS and is diagnostic for the loss of $C_6H_7O_4$. This fragment, corresponding to the α,β-unsaturated portion of **4**, would only be expected for the β-eliminated open chain product **4**.

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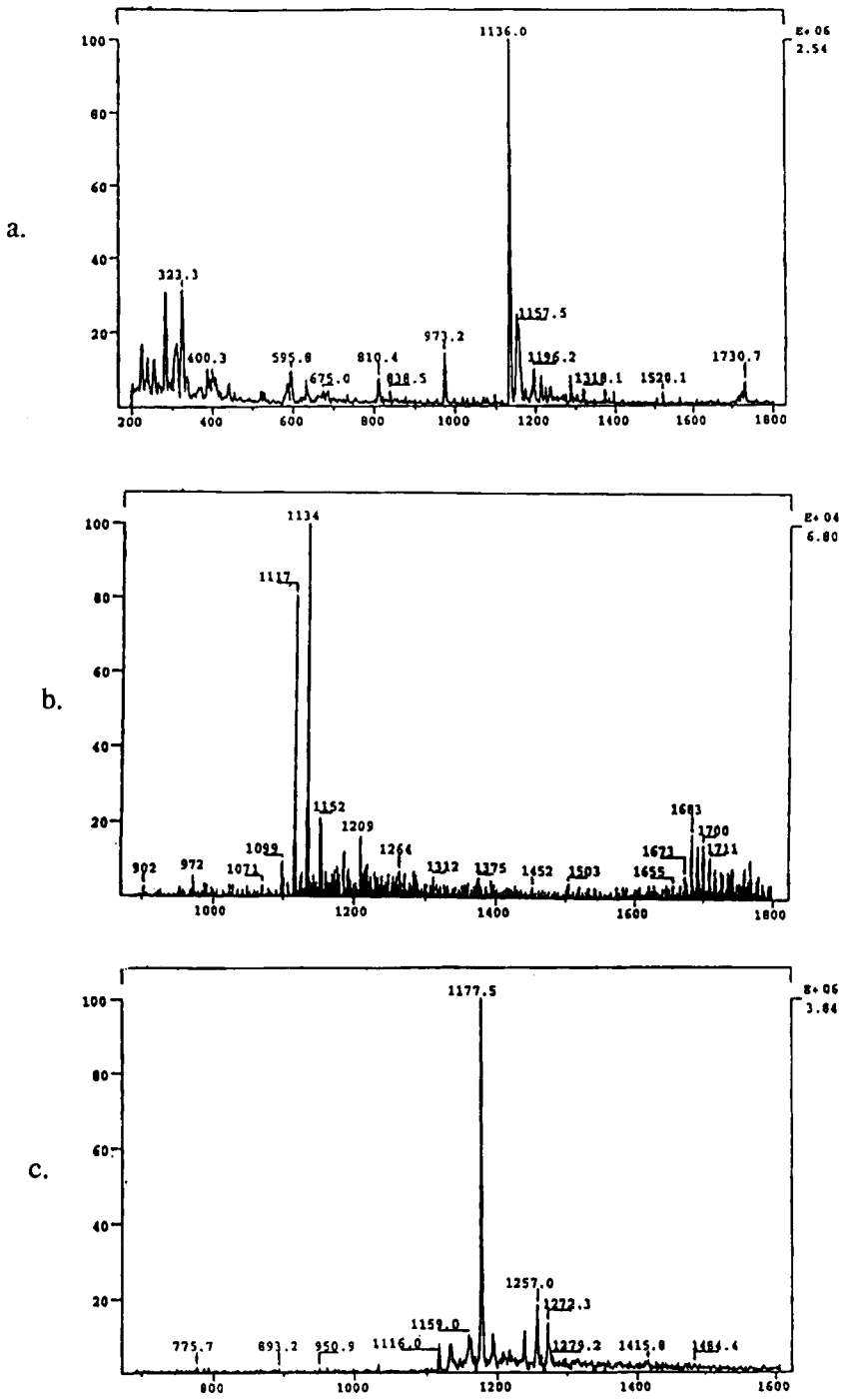

Figure 1. Electrospray mass spectra of (a) β-CD **1**, (b) β-cyclodextrin monoaldehyde **3**, and (c) hydrazone derivative **7**.

Mechanistic Considerations. We noted that the use of 1 equiv of *N*-methylmorpholine *N*-oxide (NMMNO) in the oxidation of the tosylate **2** resulted in β-elimination product **4**, although the presence of 1 equiv of *N*-methylmorpholine (NMM) itself during the oxidation of **2** to **3** did not induce β-elimination. Perhaps proximity effects may play a role in accelerating β-elimination with the *N*-methylmorpholine *N*-oxide route, since the *N*-methylmorpholine free base under these circumstances is eliminated in close proximity to the acidic α-proton of the aliphatic cyclodextrin aldehyde and could act as a general base[33] (Figure 2a) for the catalysis of this elimination reaction. Host–guest complexation of the eliminated base (Figure 2b) may thus contribute further to the catalysis of β-elimination in this mechanism, as it is known that complexation reactions between cyclodextrins and their organic host can occur in DMSO solution.[34] We performed NMR chemical shift monitoring experiments for the forward and reverse titrations of *N*-methylmorpholine guest with cyclodextrin host in d_6-DMSO (Table 3). We found that 1:1 binding occurs between NMM and β-CD with a K_a of approximately 75 M^{-1} as determined by the method of Rebek et al.[35] Binding affinities for trimethylamine and β-cyclodextrin

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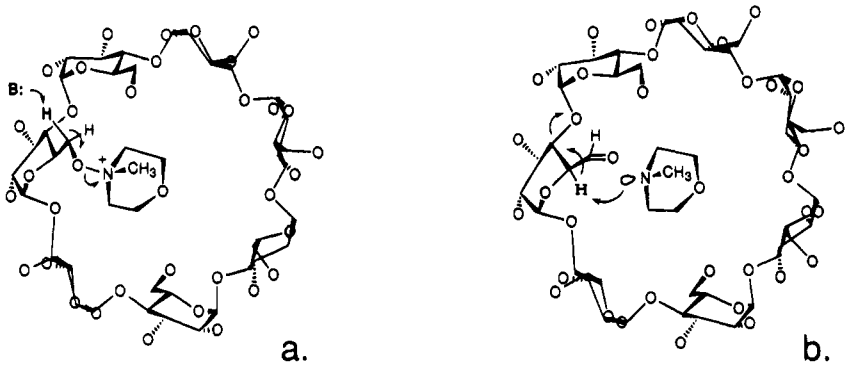

Figure 2. Proposed reaction pathway to the β-elimination product *4* of β-cyclodextrin tosylate **4** via the *N*-oxide route: (a) *N*-methylmorpholine *N*-oxide adduct, (b) transient complex of cyclodextrin aldehyde and *N*-methylmorpholine in vicinity of the acidic α-proton of the 6-β-cyclodextrin aldehyde **3**.

Table 3. Comparison of Binding Constants for Organic Bases and the Corresponding *N*-Oxides with β-Cyclodextrin in DMSO Solution

entry	guest	K_a (M^{-1})	titration method
1	*N*-methylmorpholine	75	forward[a]
2	*N*-methylmorpholine *N*-oxide	50	reverse[b]
3	trimethylamine *N*-oxide	98	reverse[b]

[a] Followed NMR chemical shift of the guest while titrating guest to stock solution of host. [b] Followed NMR chemical shift of guest while titrating host to stock solution of guest.

could not be determined due to the inability to ascertain reliably the concentration of trimethylamine in solution.

Although the binding affinity of *N*-methylmorpholine and β-cyclodextrin is low and 1 equivalent does not lead to β-elimination, higher amounts of *N*-methyl morpholine (10 equiv) can induce efficient β-elimination of the aliphatic β-cyclodextrin aldehyde **3** under otherwise identical conditions (Table 2). This observation suggests that the effective molarity of the cyclodextrin:*N*-methylmorpholine complex may be increased immediately subsequent to initial oxidation when using *N*-oxides for this conversion.

The possibility remains, however, that the excess *N*-oxide itself can induce β-elimination of the cyclodextrin aldehyde formed by this reaction. The addition of 10 equiv of *N*-methylmorpholine *N*-oxide to the isolated cyclodextrin aldehyde **3** also induces β-elimination to **4**. Thus, we conducted NMR titration experiments to determine the binding affinity of *N*-methylmorpholine *N*-oxide to β-cyclodextrin and found a K_a value of around 50 M^{-1} (Table 3). Binding studies with cyclodextrin and trimethylamine *N*-oxide, which also induces β-elimination during the oxidation of **2**, were conducted, and the K_a for the cyclodextrin:trimethylamine *N*-oxide complexation was found to be 98 M^{-1} (Table 3). Thus, the *N*-oxide when bound inside the cyclodextrin cavity can induce β-elimination as observed with a large excess of the corresponding parent base.

Although we cannot discern which of these mechanisms or combinations of mechanisms is operating in this case, β-elimination product **4** can be efficiently obtained by using an amine *N*-oxide (e.g., TMA-NO, NMM-NO) for this conversion or completely avoided to yield aliphatic monoaldehyde **3** by using a hindered amine base (e.g., Hunig's) as the catalyst for this conversion.

Summary

The described oxidation procedure provides a useful route to an electrophilic β-cyclodextrin for attachment to solid phases, polymers, or biomolecules through the 6-hydroxyl primary rim. This conversion is brought about by the nucleophilic displacement of cyclodextrin monotosylate with DMSO in the presence of a hindered amine base. The β-elimination product can be obtained by the addition of trimethylamine *N*-oxide or *N*-methylmorpholine *N*-oxide to the reaction mixture.

We also expect these procedures to be applicable to the synthesis of the corresponding monoaldehydes or β-elimination products of α-cyclodextrin, γ-cyclodextrin, and other carbohydrate oligomers as well. The utility of these β-cyclodextrin aldehyde derivatives is currently under investigation, and their use in bioconjugation applications will be reported in due course.

Experimental Section

General. All ^1H NMR spectra were recorded on either a ChemMagnetics A-200 at 200 MHz, a Gemini 300 at 300 MHz, or a GE 500 at 500 MHz. All ^{13}C spectra were obtained on a GE 500 at 125.7 MHz. All starting materials, unless otherwise specified, were obtained from the Aldrich Chemical Co. and used without further purification. Analytical HPLC was performed on a Waters System equipped with a Model 600 multisolvent delivery pump equipped with a Model 481 UV detector, a Waters U6K injector, and a Waters 740 data module. Preparative work was conducted on either the Waters system described above or on a Rainin system with HPXL or Rabbitt pumps equipped with a UV-D Model multiwavelength UV detector, a Rheodyne injector, and Rainin DYNAMAX DA, EM, and Chromplot Software on a MacIntosh SE-30 PC. RP-HPLC columns used for preparative and analytic separations were DYNAMAX-60A 41.4 mm i.d. radial compression column (C-8) or DYNAMAX-60A 4.6 × 250 mm columns, respectively. CH analyses were obtained by ORS Chemical Analysis Group (Whitesboro, NY). IR spectra were obtained on a Perkin-Elmer 298 IR spectrophotometer. Mass spectra were obtained on a Finnigan mass spectrometer using (+) PDMS (BIOION), FAB, EI, CI, or ESIMS techniques. Unless otherwise specified, silica gel TLC was conducted using normal-phase plates precoated with silica gel 60 F_{254} obtained from Merck (Darmstadt, FDR). Plates were developed using $(NH_4)_2Ce(NO_3)_6$ in 10% aqueous H_2SO_4.

Synthesis. β-Cyclodextrin Monoaldehyde 3 (DMSO Mediated Oxidation of 2). Monotosylate **2** of β-cyclodextrin was prepared according to the method of Petter or Melton.[13,14] The monotosylate was either precipitated[14] or purified by preparative RP-HPLC using a gradient separation at 40.0 mL/min on a Rainin DYNAMAX radial compression column. The gradient used for this separation was follows: a linear gradient from 90/10 H_2O/CH_3OH initial condition to 60/40 H_2O/CH_3OH after 20 min, to 45/55 H_2O/CH_3OH by 30 min, followed by ramping to 0/100 H_2O/CH_3OH by 35 min total elapsed time. The monotosylate eluted at 20.7 min using this gradient with UV detection at λ 230 nm. The solvent was removed at reduced pressure, and the remaining solid was subjected to high vacuum overnight. The monotosylate (1.0 g, 0.776 mmol) was then

dissolved in 20.0 mL of DMSO. To this solution was added 0.5 equiv of Hunig's base (0.060 g, 0.388 mmol). The reaction mixture was heated for 72 h at 70–80 °C under sealed tube conditions or under nitrogen. After the reaction mixture was cooled to room temperature, the crude product was precipitated with acetone (200 mL) and cooled to 0 °C. The resulting solid was isolated by vacuum filtration, resuspended in acetone (100 mL), and followed by filtration; this step was repeated 2×. Tosylate **2:** PDMS obsd 1311.7, calcd 1310.2 ($M + Na^+$); ESIMS obsd 1289.2, calcd 1288.2 ($M + H^+$); ^1H NMR d_6-DMSO δ 7.7 (d, 2H, 14 Hz), 7.4 (d, 2H, 14 Hz), 5.6 (broad s, 6H), 4.85 (d, 1H, 2 Hz), 4.75 (d, 1H, 3 Hz), 2.45 (s, 3H); ^{13}C NMR (125.6 MHz) d_6-DMSO δ 144.8, 132.7, 129.9, 128.1, 127.6, 125.5, 102.0, 81.5, 73.1, 72.1, 72.4, 72.0, 59.9, 21.2; TLC (1/1 mixture of 10:8:3 *n*-butanol/ethanol/water and 12:3:4 butanone/methanol/acetic acid): R_f 0.6; yield 7.5% on a 60.0 gram scale. Monoaldehyde **3:** PDMS obsd 1155.5, calcd 1155.9 ($M + Na^+$); ESIMS obsd 1133.9, calcd 1134.0 ($M + H^+$); ^1H NMR (300 MHz) d_6-DMSO δ 9.7 (s, 1H), 5.75 (broad m, 14H), 4.85 (m, 7H), 4.48 (m, 6H), 3.6 (m, 14H), 3.4 (broad m, 7H); ^{13}C NMR (125.6 MHz) crude reaction mixture in d_6-DMSO, excluding tosylate peaks. d_6-DMSO δ 198.2, 120.19, 87.5, 82.5, 81.7, 81.5, 73.072.7, 72.4, 72.0, 68.9, 59.9, 59.6; TLC (1/1 mixture of 10:8:3 *n*-butanol/ethanol/water and 12:3:4 butanone/methanol/acetic acid) R_f 0.5; yield 85% on a 1.0 g scale.

β-Elimination Product 4 (TMANO Mediated Oxidation of 2). To a solution of monotosylate **2** (1.0 g, 0.77 mmol) in 20.0 mL of DMSO, anhydrous[18] trimethylamine *N*-oxide (5.39 mmol, 0.406 g), *or N*-methylmorpholine *N*-oxide (5.39 mmol) was added. The resulting solution was heated to 70 °C under sealed tube conditions or under nitrogen atmosphere for 16 h. After the reaction mixture was cooled to room temperature, the product was precipitated with acetone (200 mL) and cooled to 0 °C. The resultant solid was isolated and resuspended in acetone (10 mL) and filtered; this step was repeated 4×. The filtered solid was then dried under high vacuum at room temperature overnight: PDMS obsd 1156.2, calcd 1155.9 ($M + Na^+$) ESIMS obsd 1135.3, calcd 1134.0 ($M + H^+$); ^1H NMR (300 MHz) d_6-DMSO δ 9.3 (s, 1H), 6.23 (d, 1H, 3 Hz), 5.62 (d, 1H, 4 Hz), 5.4 (s, 1H), 5.2 (d, 6H, 6 Hz), 3.9 (m, 7H), 3.65 (m, 13H); ^{13}C NMR (125.6 MHz) of crude reaction mixture in d_6-DMSO, excluding tosylate peaks d_6-DMSO δ 187.4, 147.8, 124.4, 101.9, 100.4, 99.9, 96.8, 92.1, 81.6, 79.7, 79.4, 76.4, 76.2, 74.3, 73.1, 72.5, 72.1, 71.7, 79.3, 65.5, 60.3, 59.9; TLC (1/1 mixture of 10:8:3 *n*-butanol/ethanol/water and 12:3:4 butanone/methanol/acetic acid) R_f 0.3; yield 100% on a 1.0 g scale.

Characterization of Derivatives. Reduction of 3 or 4. Aldehyde **3** or **4** (0.1 g, 0.088 mmol) was dissolved in 1.0 mL of H_2O. To this solution was added 5.0 mL of CH_3OH. While the solution was stirred under N_2, 100 mg of $NaBH_4$ (2.63 mmol, 30.0 equiv) was added. After this mixture was allowed to stir for 1 h, an additional 30.0 equiv (100 mg) of $NaBH_4$ was added. This solution was allowed to stir for an additional hour. The reaction was then quenched with 50.0 mL of acetone, and the resulting solid was filtered and dried under high vacuum.

Reduction product of **3**: TLC (1/1 mixture of 10:8:3 n-butanol/ethanol/water and 12:3:4 butanone/methanol/acetic acid): R_f 0.4. Product **6** (reduction of **4**): TLC (1/1 mixture of 10:8:3 *n*-butanol/ethanol/water and 12:3:4 butanone/methanol/acetic acid): R_f 0.2.

Hydrazone Derivative 7. Cyclodextrin aldehyde **3** (100 mg, 0.088 mmol) was dissolved in 5.0 mL of 1,1-dimethylhydrazine. After this mixture was allowed to stir for 6 h, the excess solvent was removed in vacuo and the crystalline residue was collected. After vacuum pumping overnight, this material was recrystallized from CH_3OH: $(M + H)^+$ $C_{44}H_{74}N_2O_{34}$ PDMS obsd 1178.9, calcd 1176.1; ESIMS obsd 1177.4, calcd 1176.1; ^1H NMR (d_6-DMSO) δ 5.74 (m, 6H), 5.65 (s, 1H), 4.8 (7H), 4.45 (6H), 3.6 (broad s, 7H), 3.3 (broad s, 14H), 2.73 (s, 1H), 2.2 (s, 1H). CH Anal. Calcd for $C_{44}H_{74}N_2O_{34}\cdot 5H_2O$: C, 41.77; H, 6.69; N, 2.21. Found C, 41.66; H, 6.27; N, 2.64.

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Supplementary Material Available: Saturation plots for titration of β-cyclodextrin with *N*-methylmorpholine, *N*-methylmorpholine *N*-oxide, and trimethylamine *N*-oxide. ^1H NMR spectra of 6-β-cyclodextrin monoaldehyde **3** and β-elimination product **4** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.