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Facile Preparation of the β-Cyclodextrinyl Aldehyde

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Abstract: This paper describes the synthesis and characterization of the 1° - side β-Cyclodextrinyl Monoaldehyde in two steps from β-cyclodextrin.

Cyclodextrins have found wide utility in the synthesis of artificial enzymes due to their ability to bind compounds in aqueous solution.[1] In order to expand this area of chemistry, the synthesis of functionalized cyclodextrins on a preparative scale is necessary.[2] While the net reduction of cyclodextrin's primary side hydroxyl groups is known,[3] selective oxidation reactions are almost unknown.[4] A synthesis of the α-cyclodextrinyl aldehyde has been reported by photolysis of the primary side azide and ninhydrin oxidation of the 1°- side amine.[5] We now report an experimentally simpler synthesis involving the conversion of the β-cyclodextrin 1°- side monotosylate directly to the 1°- side aldehyde using the Nace reaction.[6,7]

β-Cyclodextrin can be converted to the monotosylate by tosylation using various procedures.[8] We reasoned that a homogeneous sample of the monotosylate would afford selectively the monoaldehyde via oxidation with DMSO.[9] A solution of **1** (14 mM) in DMSO-d_6 was thus heated at 135°C and the reaction was monitored by PMR. The disappearance of the aromatic tosylate peaks and concomitant appearance of peaks corresponding to tosic acid and **2** was observed. The half-life of the reaction was approximately 15 min based on the disappearance of the tosylate. Additional aldehyde peaks, apparently resulting from the decomposition of **2**, appeared after longer reaction times (40 min). Co-addition of a non-nucleophilic base to the reaction was expected to 1) facilitate the elimination of dimethyl sulfide from the intermediate, and 2) neutralize the acid produced in the reaction. Indeed, the addition of collidine (95 mM, 6.5-fold molar excess) essentially stopped the decomposition of the aldehyde, although the half-life of the reaction was not significantly altered.

On a preparative scale (Figure 1), **1** (1.0 g, 7.8 x 10^{-4} mols), recrystallized 3 times from hot water, was dissolved in DMSO (10 mL). Collidine (1 mL, 10-fold molar excess) was added and the yellow solution was heated at 135°C for 1.5 h. The resulting dark brown solution was added dropwise to acetone (100 mL) and the precipitate collected

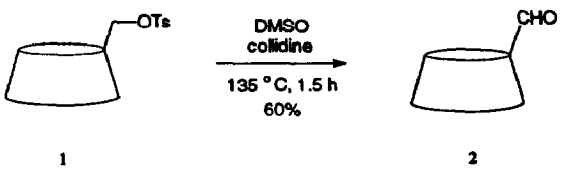

Figure 1. Synthesis of β-Cyclodextrinyl Monoaldehyde

under vacuum. This solid was then dissolved in water (10 mL) with warming and precipitated from 95% ethanol (100 mL) to afford **2** as a colorless solid (57 mg, 64%). This material has resisted our efforts at crystallization to date and appears to contain only β-cyclodextrin as a minor impurity as determined by PMR integrations. Not surprisingly, the aldehyde has similar solubility characteristics as β-cyclodextrin.

The sample thus obtained has been fully characterized as monoaldehyde **2**. PMR in DMSO-d_6 shows relevant peaks at 9.7 ppm (C<u>H</u>O), 4.2 ppm (C<u>H</u>CHO) and typical peaks corresponding to β-cyclodextrin. CMR of the sample also displays an aldehyde peak at 198 ppm. Mass spectral analysis of the sample shows a molecular ion peak at *m/e* 1133. Microanalysis of the sample calculated for $C_{42}H_{68}O_{35}\cdot 8H_2O$: C, 39.50; H, 6.63; found: C, 39.40; H, 6.84. Characterization was further confirmed by formation of the bisulfite addition product of **2**.[10] This product was formed by the addition of excess $NaHSO_3$ to a saturated aqueous solution of **2**. The bisulfite product has also been characterized by PMR, CMR and mass spectrometry.

PMR analysis in D_2O demonstrates 100% conversion of aldehyde **2** to the covalent hydrate. This is characterized by the disappearance of the protons related to the aldehyde (C<u>H</u>O and C<u>H</u>CHO as noted above) and the appearance of a proton signal for the covalent hydrate at 5.2 ppm (C<u>H</u>$(OH)_2$). The successful generation of the bisulfite derivative, carried out in water, confirms an equilibrium between the covalent hydrate and the aldehyde form.

In summary, we report a preparatively useful method for the synthesis of β-cyclodextrin monoaldehyde. This synthesis can be done easily in two steps from β-cyclodextrin incorporating a DMSO/collidine oxidation. Additional chemistries utilizing this method can be envisioned, some of which are the focus of current studies in our laboratory.

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8. (a) Matsui, Y.; Okimoto, A. *Bull. Chem. Soc. Jpn.* **1978,** *51(10),* 3030. (b) Repeated recrystallization from water affords the monotosylate in good homogeneity. Alternatively, chromatography on a charcoal column can provide excellent fractionation (Private communication, Dr. Russell Petter and Christopher T. Sikorski, Ph.D. Thesis, University of Pittsburgh, 1992).
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