Laser-induced, one-step synthesis of cyclodextrin carboxylic acids and their esters

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α- and β-Cyclodextrin 6-azides (or 6A,6D-diazide) when subjected to laser irradiation followed by mild hydrolysis, lead, via the aldehyde, to small yields of corresponding acids, or in presence of alcohol to methyl or ethyl esters. The structures of compounds obtained have been identified using ESI mass and NMR spectroscopy.

Keywords: Cyclodextrin, laser-assisted, solvolysis, NMR, mechanism

Despite constant progress and sophistication of synthetic methods, the selective functionalization of cyclodextrins (CDs), an important class of supramolecular compounds involved in a wide spectrum of practical applications1,2, remains of huge interest. In particular, the selective and controlled oxidation of the alcohol groups on the primary rim, offers possibilities for further couplings of those compounds to, for example, biological targets through the created carbonyl function3,4.

The oxidation of simple CDs by using, for example, a Dess-Martin periodinane (DMP) reaction or Swern oxidation, affords monoaldehydes5. When more complex CDs are used in multistep syntheses, somewhat more complicated blocking/deblocking reaction sequences are usually required6.

In previous papers in this series, on the laser induced transformation of another family of supramolecules, calixarenes-crowns7-9, their clean transformation was reported according to the photo-Clayson reaction pathway10. The synthesis and spectroscopic analysis of amino-cyclodextrins11 via intermediate aldehyde 5 formation, using laser-assisted oxidation13 (Figure 1). This pathway, modelled on Horton’s seminal works12-15 on photochemical transformation of sugar and cellulose azides into 6'-aldehyde derivatives, offered somewhat shorter access to the CD-carboxylic acids, especially to the dicarboxylic acids of known stereochemistry. The analogous transformation of azido derivatives into carbonyl containing compounds under conventional (thermal) or microwave-assisted heating was unsuccessful. Simultaneously, the photochemical transformation of one of the starting azides, using a mercury arc tube, also did not produce the expected CD-derived carbonyl in detectable yields.

Experimental Section

Materials and Methods

Starting CD-azides were prepared according to Hocquelet’s thesis procedures16 and our group’s related papers11,12.

The NMR spectra of selected products were recorded on 200, 300 and 400 MHz instruments and mass spectra on a LCQ Advantage MCS Thermo Finnigan (San Jose, Cal., US) using the spray ionisation mode in methanol or methanol/water solutions. With the exception of a source temperature of 200°C, capillary voltage of 23-25 V, and tube lens voltage of 55 V, the parameters can be found in previous work10. The IR spectra were recorded in Nujol on HP instruments.

Laser photolysis of azides 1b and 2a

Azides 1b or 2a, in solutions of water, methanol or ethanol (ca. 10 mg, 10:3 molar ratio) were placed in 9 mm × 9 mm × 15 mm quartz cells which were previously washed with water and dried, and were used separately in the laser photolysis experiments.

An Nd:YAG laser operating at a wavelength of 355 nm and an impulse duration of 5 ns, was stabilised for ca. 30 min prior to being used for photolysis. The beam’s energy was 130-135 mJ on the solution and 170 mJ at the cell entry levels; however, by the end of a photolysis reaction period of 30-45 min the energy output had dropped to only 110 mJ. Just after 1 min of photolysis and during the entire photolysis
experiments, slight solvent bubbling was observed. The total time of operation, from preparation of the solution and laser warm-up, to reaction termination, was around 90 min per sample. The reaction mixture was treated with a 0.1 N HCl solution \((pH \approx 4)\) at RT for 24 hr and retreated with the laser for 30 sec. The solvents were then evaporated under reduced pressure, and the product mixtures analysed via spectroscopic methods after the initial purification via HPLC of the organic phase.

The reaction carried out in water led to the carboxylic acid, whereas when performed in ethanol or methanol it led to CD ethyl or methyl esters, respectively.

**Starting azides**

\(\beta\)-CD monoazide (1160) (alt. name: 6-azido 6-deoxy \(\beta\)-cyclodextrin), 1b: This compound, obtained according to reference 16 contains a significant quantity of starting cyclodextrin (20-35%) which was not removed at this stage. This somewhat explains the lack of NMR signal integration accuracy in this series. IR: 2102 cm\(^{-1}\) \((N_3)\); \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 5.1, 4.0, 3.85-3.97, 3.68, 3.61; \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 97-98.7, 80.6-81.2 (\(C_3\), \(C_4\)), 80.3 (\(C_4\)), 78.6-79.6 (\(C_2\), \(C_3\), \(C_4\)), 70.8-72.4 (\(C_5\)).

\(\alpha\)-CD diazide (1022) (alt. name: 6A,6D-diazido 6A,6D-dideoxy \(\alpha\)-cyclodextrin), 2a: This compound was obtained according to references 11, 12, 14-16. IR: 2102 cm\(^{-1}\) \((N_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.12, 5.07, 5.06, 3.7-3.99, 3.4-3.7, 3.1-3.2; \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 98.3-99.3 (\(C_4\)), 80.4-82 (\(C_2\), \(C_3\)), 80.1-82 (\(C_4\)), 70.7-70.9, (\(C_5\)), 71.1, 70.8-72.4 (\(C_5\)), 52 (\(C_6\)).

**CD-carboxylic acids**

\(\alpha\)-CD diacid (1022) (alt. name: 6A,6D-dicarboxy-\(\alpha\)-cyclodextrin), 3a. Yield: 11%; MS: \(m/z\) 1022 (MNa\(^{+}\)). Purification of the analytical sample was performed via reverse-phase HPLC (C 18, water-acetonitrile system). \(^1\)H NMR (200 MHz, D\(_2\)O): \(\delta\) 4.95 (centre), 4.10, 3.2-3.4, 3.5-3.9; \(^13\)C NMR (100 MHz, D\(_2\)O): \(\delta\) 171.5, 101.0-101.5, 81.3, 80.8, 73.2, 72.8, 71.5, 71.8, 60.1, 59.5.

**CD-methyl dicarboxylates**

In this reaction, a mixture of 4a and 5 was obtained and was not separated. Attempts to purify either of these compounds failed.

Major product: \(\alpha\)-CD methyl dicarboxylate (1050), (alt. name: dimethyl-6A,6D-dicarboxy-\(\alpha\)-cyclodextrin), 4a. Yield: 15%; MS: \(m/z\) 1050.35 (MNa\(^{+}\)).

Minor product presence: \(\alpha\)-CD-di aldehyde, (alt. name: 6A,6D-diformyl-\(\alpha\)-cyclodextrin), 5. Yield: 5% (est.); MS: \(m/z\) 969.15 (MH\(^{+}\)).

**Mixture of 4a and 5.** \(^1\)H NMR (200 MHz, DMSO-\(d_6\)): \(\delta\) 9.5 (aldehyde), 5.5-5.9, 4.3-4.65, 4.2, 3.6-3.9, 3.1-3.8, 3.4 (OCH\(_3\)); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 197.5 (aldehyde C=O), 171.4 (ester C=O), 100-101.5, 87, 81, 73, 72 (centre), 60.

**CD-ethyl mono carboxylates**

\(\beta\)-CD ethyl carboxylate, (alt. name: ethyl 6-carboxy-\(\beta\)-cyclodextrin), 4b. Yield: 12%; MS: \(m/z\) 1201 (MNa\(^{+}\)). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 4.8-4.95, 4.15, 2.6-3.2, 1.5; \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 165.5 (C=O), 101-102.5, 80 (centre), 70-75, 52, 16.

**Microwave or conventional heating of azide**

The 10-2 molar ratio water or ethanolic solution of azides (1 or 2) was refluxed for 30 or 60 min, or
exposed to microwave assisted heating on a Discover CEM in 10 mL vessel (Magneton frequency 2455 MHz, 200 W power output). Typical experimental conditions: temperature 150°C max., pressure 5 bar, reaction time 15-20 min followed by 20-25 min of cooling. Under both reaction conditions no carbonyl containing products were detected.

**Photochemical degradation of azide**

The 10-2 ratio molar water solution of 1b was reacted in a Hanovia PCR 1L (International Scientific, Hanovia, 2001) photochemical reactor equipped with a medium pressure mercury arc tube in a quartz vessel. Reaction times of 30, 120 and 240 min did not produce any carbonyl containing compounds.

**Results and Discussion**

Following the series of decompositions of CD azides under laser, microwave, thermal and photochemical, conditions only the laser-assisted reaction was able to produce carbonyl-function containing derivatives and that too only in low yields. In water, the carboxylic acid was obtained; however when methanol or ethanol were used as solvent for flash-laser solvolysis, the corresponding esters were formed. The important aspect of this reaction is its formation, despite overall low (11-15%) transformation yields. In practice, after solvent evaporation, the CD-carboxylic acid was obtained. The simultaneous presence of aldehyde and methyl ester in one reaction mixture could be related to the presence of water in the methanol used as solvent in this photolysis. The first indication that carbonyl containing compounds were formed, was the disappearance of the characteristic IR absorption band at ca. 2100 cm⁻¹ typical of azides.

Among these results, the transformation of a "native" (meaning with free hydroxyls on all secondary and remaining primary carbons) 6A,6D-diazido α-CD 2a into a corresponding 6A,6D – α-CD dimethyl dicarboxylate 4a (MNa⁺ ion at m/z: 1050.3) with 15% yield is worth mentioning. This compound, however, also showed the presence of a protonated dialdehyde 5 ion at m/z 969.15 (MNa⁺ ion), which is an important feature for suggesting the reaction intermediate. In this hypothesis, the formation of a nitrene intermediate from the azide is followed by its acid hydrolysis and oxidation/solvolysis, for example, in methanol reactions (Scheme I). Similarly, the same reaction in water led rather to the production of dicacid 3a (MNa⁺ ion at m/z 1022). The hypothesized nitrene intermediate in the decomposition of some aromatic azides using MALDI has already been suggested by Chen¹⁸.

In the "native" β-CD series mono azide 1b (6-azido β CD) was transformed into the corresponding ethyl ester 4b when laser photolysis was performed in ethanol. The presence of molecular ion at m/z 1201 confirmed this reaction. For the benzylated or methylated CD similar oxidations were unsuccessful. It seems that the presence of secondary hydroxyls on the CD scaffold helps in the formation of carbonyl groups. In both reactions, for both α- and β- CD, an important quantity of polymeric material, as well as of some starting CD, was isolated.

In thermal or microwave assisted transformations of azides, complex mixtures of products were obtained, none having carbonyl functions. The reaction of CD-azides performed with help of a photochemical reactor (medium pressure Mercury arc) led only to the formation of polymeric material. This result could be explained by the UV output characteristic of this reactor, with 365 nm (16%) and 45% of intense radiations at 400-435 nm and 546-590 nm, the conditions were not suitable for the formation of carboxylic acid, especially when compared to the more energetic, focalized laser we used.

All compounds in this study showed satisfactory partial spectral characteristics; although the starting azides, carboxylic acids and esters were mainly characterised by mass spectrometry (ESI, PI) and only supported by NMR. These last spectra of the products are in agreement with those already obtained by our group and are comparable to known CD-carboxylic acid derivatives¹⁴⁻¹⁷.
Assuming that the CD azides are quite popular and easily accessible, synthetic intermediates, for example in the synthesis of CD-amines, the oxidation of the C-6 hydroxyl via the azide route described in this paper, offers another alternative to the synthesis of carboxylic acid derivatives of sugars. However, laser reactor availability remains an important limitation to wider use of the pathway discussed in this paper.

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