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ORIGINAL ARTICLE

Regioselective alkanoylation of cyclodextrins

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Abstract The regioselective transesterification of native α- and β-Cyclodextrins (CDs) with vinyl acetate and vinyl laurate is presented in this paper. The reactions were carried out in dimethyl sulfoxide by using low molecular weight salts (Na_2HPO_4 and NaCl, respectively). MALDI-TOF mass spectrometry and NMR analysis were applied to investigate the chemical structure and the degree of the modification of the final products. Results show that these salts catalyze regioselective transesterification between β-CDs and vinyl laurate aiming for the secondary C-2 hydroxyl group. The synthesis and separation of β-CD-laurate derivatives leads to a mixture of mono-2-*O*-dodecanoyl-β-CD and native β-CDs. Unreacted β-CDs could be selectively removed enzymatically by cyclodextrin glucosyl-transferase (CGTase) and β-amylase.

Keywords Acetylation · Alkanoylation · Cyclodextrins · Chemical modification · Dodecanoylation · Regioselectivity

Abbreviations

AGU	Anhydroglucopyranose unit
CCA	Cyano-4-hydroxycinnamic acid
CD	Cyclodextrin
CGTase	Cyclodextrin glucosyl transferase
DMSO	Dimethyl sulfoxide
FENC	Fast evaporating nitro-cellulose
FT-IR	Fourier transform infrared spectroscopy
HSQC	Heteronuclear single quantum coherence
MALDI-TOF MS	Matrix assisted laser desorption/ionisation time of flight mass spectrometry
NMR	Nuclear magnetic resonance
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography

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Introduction

CDs have a high ability to form inclusion complexes with various guest molecules which can have highly altered properties such as solubility, stability, reactivity, volatility and bioavailability compared to that of the guest molecule alone. These properties are currently used in numerous applications in the pharmaceutical, agro-chemical, food and chemical industries [1]. Amphiphilic CDs are proposed for various applications e.g. as drug carrier systems and for deposition on electrodes as part of biosensors [2, 3]. Furthermore, cyclodextrins and their derivatives have become the molecules of choice in the area of analytical chemistry for the separation of structural, positional, and stereo isomers [4]. Therefore in the previous decades, research into chemical derivatisation of CDs has increased. Recently, there has been great interest in modifying CDs by grafting long hydrocarbon chains onto one face of the CD to obtain an amphiphilic molecule [1d, 5]. Hereby not only the ability of the CDs to act as host for inclusion of guest molecules in their cavity, but also the ability to form larger molecular aggregates can be exploited. However, the discrimination by selective

reactions between the primary and secondary hydroxyl groups of CDs is complicated by the statistical and steric problem imposed by the torus structures and the large number of hydroxyl groups positioned at C-2, C-3 (the two secondary ones) and C-6 (the primary one) on each glucopyranose unit [6, 7]. The hydroxyl groups on C-2 are only slightly less reactive than those on C-6, leading to poor selectivity [8]. It is difficult to obtain exclusive reaction at one position with no side reactions at the other hydroxyl positions [9–11]. Acetylated CDs have been prepared by a well known method in the carbohydrate chemistry, by treatment with acetic anhydride in pyridine [10, 12] and other types of catalysts [13], however, with no regioselectivity [10]. Recently, we have shown that CDs can be used as acyl acceptors in enzyme-catalysed reactions [14], and Wouessidjewe et al. [15] have reported nanoparticles formed by hexanoate and decanoate β-CD esters whose substitution degree ranges from 2 to 7 and 4 to 8, respectively. These products were preferentially substituted on the C-2 position by the corresponding acyl chain. Dicke [16] has reported regioselective acetylation of β-CD in DMSO by vinyl acetate as acetylation agent and Na_2HPO_4 as a catalyst, and has shown that similar reactions may be possible via one-step reaction using low molecules weight salts [16]. However, Dicke's work was mostly focused on starches. In this paper, we will study the regioselective transesterification of native α- and β-CDs with vinyl acetate and vinyl laurate in DMSO by using low molecular weight salts (Na_2HPO_4 and NaCl, respectively). MALDI-TOF mass spectrometry, FT-IR, and NMR analysis will be applied to investigate the chemical structure and the degree of the modification of the final products.

Experimental

Materials

Pharmaceutical grade α-CD (Cavamax® W6 Wacker-Chemie GmbH, Vallensbaek, Denmark) and β-CD (Cavamax® W7 Wacker-Chemie GmbH, Berghausen, Germany) were applied. Vinyl acetate (99+% purity) was obtained from Acros Organics, Geel, Belgium. Vinyl laurate (≥98.5% purity) was provided by Fluka Chemie AG, Buchs, Switzerland. DMSO (>99% purity, Laboratory reagent grade) was obtained from Fisher Scientific, Loughborough (Leicestershire), UK. Na_2HPO_4 (>99% purity, anhydrous) was obtained from Fluka Chemie AG, Buchs, Switzerland. Isopropyl alcohol (minimum 99.7% purity, zur analyse) was gotten from AppliChem, Darmstadt, Germany. All chemicals were directly used without further purification. Maltose monohydrate was obtained from Sigma. *Bacillus macerans* cyclodextrin glucanotransferase (E.C. 2.4.1.19) ''Amano'' was obtained from Amano Enzyme Inc. Nagoya, Japan. β-amylase (E.C. 3.2.1.2) in a 2.3 M $(NH_4)_2SO_4$ suspension, type 1-B from sweet potato, was delivered from Sigma-Aldrich.

Characterization of CD derivatives

NMR

NMR spectra were recorded on a Bruker DRX600 spectrometer equipped with a 5 mm triple-axis gradient TXI (H/C/N) probe, operating at a field strength of 14.1 T.

MALDI-TOF MS

The MALDI-TOF MS analyses were carried out on a Reflex™III from Bruker, Germany. All samples were measured in reflector mode. Samples were applied to a target plate coated with nitrocellulose, also called a FENC layer. The FENC layer was made of a 1:4 (v/v) mixture of 0.1% (v/v) nitrocellulose in acetone and saturated CCA acetone solution. The FENC layer (0.25 µl) was added on the target plate and allowed to dry before the sample was added. The next layer (sample layer) was prepared by mixing dissolved CD derivatives 1:1 (v/v) with 0.1% (v/v) trifluoroacetic acid (TFA) in 33% acetonitrile saturated with CCA and 1 µl of this mixture was applied on the dried FENC layer on the target plate.

FTIR

PerkinElmer™ AutoIMAGE FTIR Microscope was used. Solid sample was put on a gold plate which was then placed in the microscope. A background scan of the gold plate was accomplished, and it was afterwards subtracted from the sample scan.

TLC

The plates used for TLC were ALUGRAM® SIL G/UV_{254} silica gel 60 sheets with a thickness of 0.20 mm from Merck, Darmstadt, Germany. The mobile phases was acetonitrile/H_2O/ concentrated aqueous NH_3 (6:3:1, v/v) as reported by Jindrich et al. [17]. The plates were visualized by spraying a solution consisting of methanol/H_2SO_4 (1:1 w/w) on to the TLC plate followed by heating up to 140 °C until black spots appeared.

General procedure for reactions of CDs with carboxylic acid vinyl esters

Synthesis of mono-2-O-dodecanoyl-β-CD

The applied method for synthesizing CD esters is based on a transesterification of a carboxylic acid vinyl ester with the hydroxyl groups of the CDs in the presence of a low molecular salt, as described by Dicke [16, 18]. The reaction scheme of β-CD and vinyl acetate is shown in Scheme 1. 4.0 g β-CD was dissolved in 20 ml DMSO and 40 mg (2% w/w) Na_2HPO_4 (the low molecular salt) was added. Afterwards 12.8 g vinyl laurate was added to the mixture, which gives the molar ratio 16 (mol vinyl ester/mol β-CD). After 70 h of the reaction, white clouds was observed in the reaction mixture. The heterogeneous catalyst was filtered off and the product solution was precipitated in isopropyl alcohol according to the original procedure from Dicke [18]. The precipitated product was filtered off and washed several times with isopropyl alcohol and afterwards dried in a vacuum oven at 50 °C for 12 h, 1.40 g white solids were obtained. The supernatant was poured into a Petri dish and placed on a heating plate with a temperature of 50 °C until all the solvent has been evaporated and the product was solidified. The product was recovered from the Petri dish and dried in a vacuum oven with a temperature of 50 °C. 3.8 g white solids were collected.

Acetylation of α- and β-CDs

The reactions between α- and β-CDs with vinyl acetates were totally comparable with the procedure of dodecanoylation of β-CDs describe above. 2.0 g of either α- and β-CDs were dissolved in 20 ml DMSO and followed by the adding of 40 mg (2% w/w) Na_2HPO_4. 2.7 g vinyl acetate was then fed up into the mixture. After 70 h of the reaction, insoluble salts were removed by filtration. The raw products were obtained by evaporating DMSO and further dried at 50 °C in vacuum, yielding 2.7 g white solids.

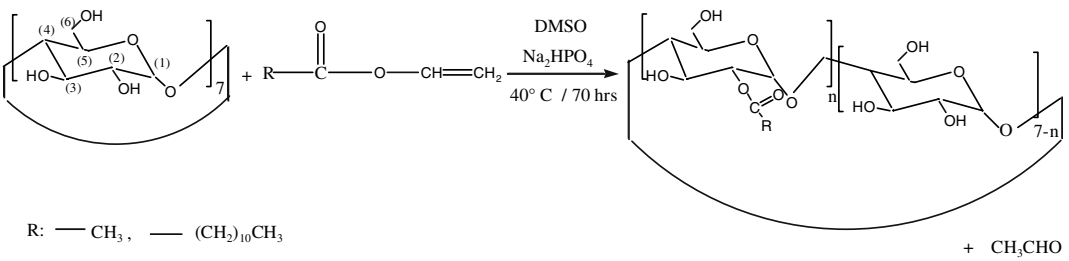
Separation of native β-CD from its derivatives of 2-O-dodecanoyl-β-CDs

5% w/w of the synthesized 2-*O*-dodecanoyl-β-CD was dissolved in water containing the buffer (pH 7) and maltose (10 mM). 100 µl crude CGTase and 20 µl β-amylase was added to the solutions. After 2 h of heating at 50 °C, the temperature was raised to 100 °C to inactivated the enzymes and the enzymes could be filtered off. A mixture of 80% v/v of ethanol in water was added into the above solutions to remove the degraded products, the precipitate was dried at 40 °C and analyzed by NMR and MS.

Results and discussion

Acetylation of α- and β-CDs

Stereoselective acetylated cyclodextrins have often been produced by multistage procedures involving protection and deprotection [19], only a few reports of successful directed acetylations have been published [6, 16]. According to Dicke [16, 18], the synthesized *O*-acetyl-β-CD was supposed to precipitate in isopropyl alcohol (iPrOH), but this could not be reproduced in this work. By concentrating the product solution under vacuum, the product could be precipitated in iPrOH, but the yield was very low. Precipitating in methylene chloride as reported by Sutyagin et al. [10] did not lead to any sediments either. In this work, the product solutions were put into a crystallization bowl at 50 °C until the solvent has been completely evaporated, and the solid products gave a yield of 57%. The mass spectrum of the *O*-acetyl-β-CD is shown in Fig. 1 (B), with the comparison of that of the native β-CD Figure 1(A), the intensities of the observed peaks are



Scheme 1 Reaction scheme for the transesterificaiton between carboxylic acid vinyl ester and β-CDs

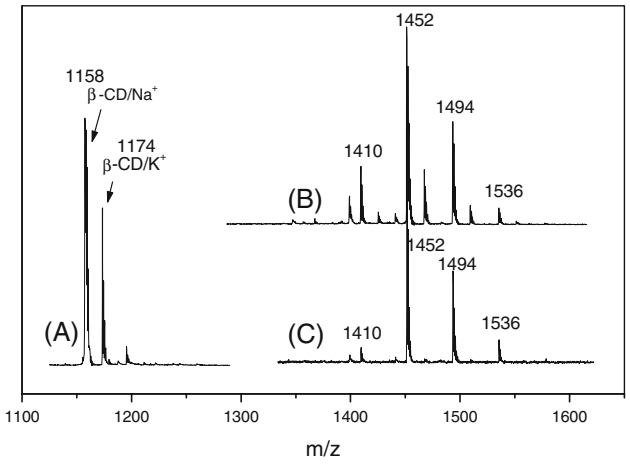


Fig. 1 MALDI-TOF MS spectrum of *β*-CD and *O*-acetyl-*β*-CDs. The value of m/z of each component is shown at the peak in the spectrum. The sodium adducts (first series) and the potassium adducts (second series) are shown. 1(**A**) native *β*-CD; 1(**B**) *O*-acetyl-*β*-CD catalyzed by Na_2HPO_4; 1(**C**) *O*-acetyl-*β*-CD catalyzed by NaCl

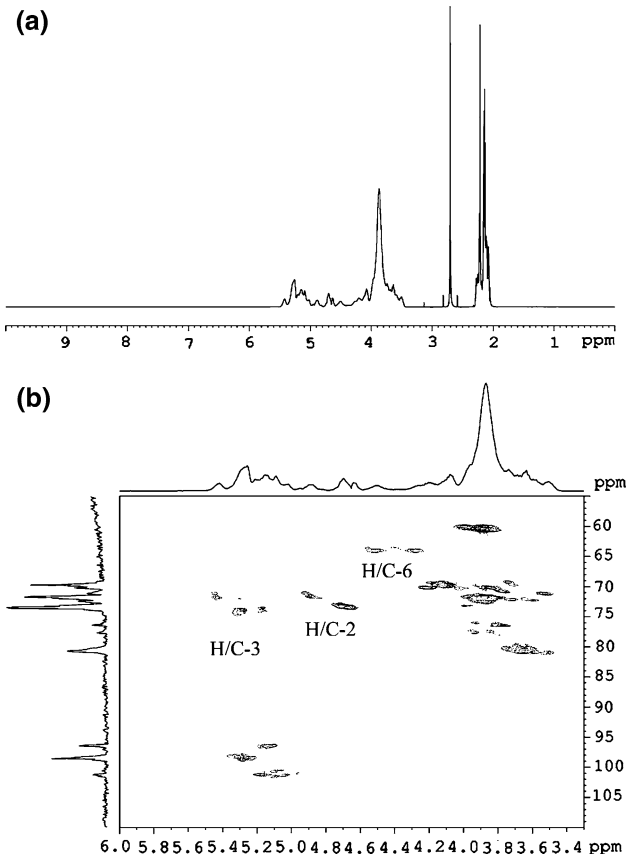


Fig. 2 Full range ^{1}H spectrum (**a**) and ^{13}C–^{1}H-HSQC NMR spectrum (**b**) of *O*-acetyl-*β*-CD (precipitated by evaporating the solvent) dissolved in D_2O and measured at 35 °C. The vertical axis is ^{1}H and the horizontal axis is ^{13}C. Correlation peaks of the esters are indicated

not necessarily a representation of concentrations [20]. It revealed a mixture with 6, 7, 8, and 9 substitutions (both sodium and potassium adducts were observed), whose R_f value obtained from TLC analysis is 0.10, 0.18, 0.25 and 0.55, respectively. Both MS and TLC analysis confirmed that no native *β*-CD was present.

The ^{1}H NMR spectrum of *O*-acetyl-*β*-CD, as shown in Fig. 2a, revealed a multitude of overlapping signals indicating the existence of several, non-equivalent glucose subunits. This may have been caused by substitution of acetyl groups in different positions on single glucose units, but also by substitution of only a part of the glucose units in a CD molecule, thus reducing or breaking the symmetry of the molecule and the chemical equivalence of the different glucose subunits [5]. Several signals for the acetate group appear with chemical shifts ranging from 2 to 2.3 ppm which indicates a mixture of CDs modified at various positions. It's not possible to ascribe the preferred position(s) of the transesterification reaction only from the ^{1}H NMR spectrum. Therefore, ^{13}C–^{1}H-HSQC NMR studies were conducted on *O*-acetyl-*β*-CD, the spectrum is shown in Fig. 2b. Observation in such a ^{13}C –^{1}H-HSQC spectrum will show cross peaks between directly bonded carbon and hydrogen atoms [21]. The spectrum of *O*-acetyl-*β*-CD showed a correlation peak of acetylated C–2, additionally correlation peaks for acetylated C–3 and C-6 were also observed. Meanwhile, several peaks for H/C-1 at δ_C = 95–103 ppm and δ_H = 4.9–5.4 ppm can be observed, implying that a mixture of molecules with varying substitution pattern is present. All of these observations indicate that an exclusive esterification on C-2 has not been obtained. However, according to Dicke [16], the acetylation of starch modified by vinyl acetate only took place on C-2, while acetic anhydride gave both acetylation on C-2, C-3 and C-6. Our results showed that the relative reactivity between the three types of hydroxyl groups within *β*-CD is not comparable with those of starches.

The synthesis of *O*-acetyl-*β*-CD by using NaCl as a catalyst resulted in the same products as by using Na_2HPO_4 as a catalyst. It is proved, by the obtained mass spectrum of the product shown in Fig. 1(C), that NaCl catalyzed transesterfication yielded a degree of modification ranging from 6 to 9 under the conditions used.

Transesterification between α-CD and vinyl acetate was also carried out, the mass spectrum of the resulted *O*-acetyl-α-CD is shown in Fig. 3. The products were obtained by both precipitation from iPrOH and crystallization via solvent evaporation. With the comparison among the above two products and native α-CD, as shown in Fig. 3, it can be seen that no raw α-CD was

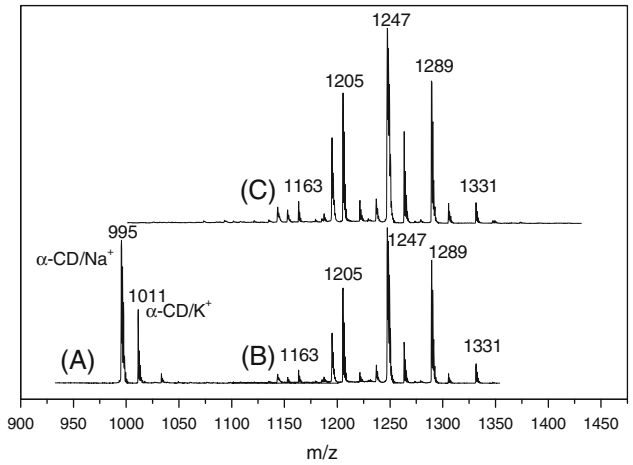


Fig. 3 MALDI-TOF MS spectra of α-CD and *O*-acetyl-α-CDs. The value of m/z of each component is shown at the peak in the spectrum. (**A**) native α-CDs. (**B**) α-CD modified with vinyl acetate and precipitated in isopropyl alcohol. (**C**) α-CD modified with vinyl acetate and crystallized by evaporating the solvent. The sodium adducts (first series) and the potassium adducts (second series, which gives less signal intensity relatively to the corresponding sodium adduct) are shown

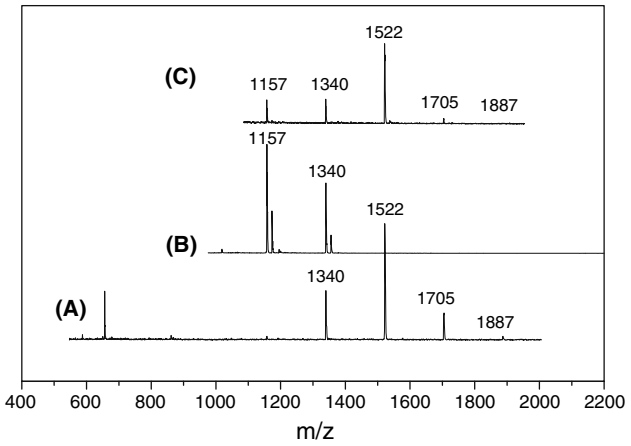


Fig. 4 MALDI-MS spectra of 2-*O*-dodecanoyl-*β*-CD before and after degradation by enzymes. The value of m/z of each component is shown at the respective peak in the spectrum. (**A**) 2-*O*-dodecanoyl-*β*-CD precipitated by evaporating the solvent. (**B**) mono-2-*O*-dodecanoyl-*β*-CD precipitated in isopropyl alcohol. (**C**) 2-*O*-dodecanoyl-*β*-CD (obtained by evaporating solvents) after enzyme action. The sodium adducts (first series) and the potassium adducts (second series)

present in the products either collected by precipitation or solvent evaporation method, and the degree of the overall substitution is ranging from 4 to 8. Because of the smaller angle between the glucopranose units in α-CD than that in *β*-CD, the hydrogen bonding network between C-2' and C-3 on adjacent glucopyranose unit would be weaker in comparing to adjacent C-2' and C-3 in *β*-CD, therefore, the regioselectivity of such acetylation reaction would be expected to decrease.

Synthesis and purification of 2-O-dodecanoyl-*β*-CD

The FTIR analysis of the synthesized 2-*O*-dodecanoyl-*β*-CD shows a distinct transmission band at 1733 cm^{-1} in the spectrum of 2-*O*-dodecanoyl-*β*-CD indicating the presence of an ester carbonyl group. The mass spectrum of 2-*O*-dodecanoyl-*β*-CD which was collected directly after solvent evaporation is shown in Fig. 4(A). The dodecanoylation of *β*-CD resulted in a product mixture with a degree of substitution ranging from 1 to 4, which is lower than the degree of substitution obtained from enzymatic reactions [14] and from dodecanoylation of starch which contains 0.7 substituents/anhydroglucopyranose unit [16]. Precipitating the reaction mixture into iPrOH leds to pure mono-*O*-dodecanoyl-*β*-CD, mixed with some unreacted native *β*-CDs as proven by the MALDI-TOF-MS spectrum shown in Fig. 4(B). The H/C-2 correlation found in the ^{13}C –^{1}H-HSQC NMR experiment of the product (precipitated by evaporating the solvent) revealed esterification only on C-2. A change in chemical shift of C-3 from 73.0 ppm to 69.5 ppm can be attributed to the esterification on C-2. Yoshimoto et al. [22] have reported an up field shift of approximately 3 ppm of C-3 upon an acetylation at C-2 of D-glucopyranoses. The enzymatic degradation of the mixture between unreacted *β*-CD and 2-*O*-dodecanoyl-*β*-CD yields a product whose MS spectrum can be seen in Fig. 4(C). It shows that the enzymes have not been able to degrade the dodecanoylated *β*-CDs. Only the peak from native *β*-CD decreases significantly. This is due to the selectivity of the enzymatic degradation caused by CGTase and *β*-amylase. The degradation products showed good solubility in EtOH/H_2O (80%, v/v%) so that only the mono-2-*O*-dodecanoyl-*β*-CD was obtained after precipitation with EtOH. It can be expected that applying this method to the mixture between unreacted *β*-CD and mono-2-*O*-dodecanoyl-*β*-CD would lead to a pure product of mono-2-*O*-dodecanoyl-*β*-CD, after removing the degradation products like glucose and maltose etc.

Conclusion

The regioselectivity is not present on the acetylation reaction on α- and *β*-CD by using Na_2HPO_4 as a catalyst. Crystallizing the products via solvent evaporation leads to better yields compared to precipitation methods. NaCl has been shown to catalyze the transesteri-

fication between β-CD and vinyl acetate resulting in products with a degree of substitution ranging from 6 to 9. Transesterification of α-CD gives a higher distribution of the degree of substitution than that of β-CD. Regioselective transesterification between vinyl laurate and β-CD gives a mixture of mono-2-*O*-dodecanoyl-β-CD and native β-CD after precipitating the reaction mixture from isopropanol. Enzymatic degradation of the unreacted components can be expected to gives rise to the final product of mono-2-*O*-dodecanoyl-β-CD in a pure form.

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