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Straightforward synthesis towards mono and bis-phosphonic acid functionalised β-cyclodextrins

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ABSTRACT

For the first time a novel class of cyclodextrins bearing phosphonic acid groups has been revealed using a new versatile methodology. These derivatives can be easily synthesised in four easy steps starting from the diol with relatively high percentage yields and no difficult purification procedures. Chemical modifications were carried out in a controlled regioselective manner using a DIBAL promoted de-*O*-benzylation, followed by a modified Horner–Wadsworth–Emmons reaction to introduce the key phosphorus moieties. Fully deprotected products could have wide applications as useful tools in biological systems as well as key building blocks in complex cyclodextrin chemistry.

1. Introduction

Cyclodextrins (CD) belong to a family of natural cyclic oligosaccharides composed of α-(1,4) linked D-glucopyranose units. The most well studied forms are α-CD, β-CD and γ-CD varying from six to eight glucose units, respectively. These supramolecular objects have acquired great interest in recent years due to their size-exclusive cavity, which is well known to encapsulate a variety of hydrophobic molecules.[1] Owing to their physicochemical properties, CDs form stable water-soluble complexes. Combining these favourable properties makes them successful pharmacological excipients; principally as bio-carriers. CDs have been cleverly employed in all routes of administration for different types of drugs; including in oral drug delivery,[2] ocular drug delivery[3,4] and also via nasal administration.[5]

This has led the innovation of many chemically modified CDs. Notably, anionic CDs have already been proven as promising molecules whereby sulfate, sulfonyl, carboxyl functional groups have been employed in chiral separations, surfactant mixed systems and in the transmembrane transportation of charged species.[6–8]

Anionic phosphate-based CDs, have been explored since well over the past decade. The introduction of the important phosphate group was first reported by either direct[9] or indirect esterification.[10] Various phosphorylating agents have been described, which often play on the difference in the chemical reactivity between the secondary and primary hydroxyl group of CD.

Mono-phosphates have been reported using a solid state synthesis where CDs were dried in the presence of metaphosphate[11] or by reaction with phosphoryl chloride.[12] The latter method led to the creation of an interesting enzyme controlled molecular recognition system, which encapsulated and released bis-guandium derivatives including antineo plastic agents. Breslow and co-workers highlighted another phosphorylating agent, diphenyl phosphorochloridate, which after catalytic hydrogenation gave the ammonium salt form after tedious recrystallisations.[13] Such compounds were evaluated for their catalytic ability in both acidic and basic conditions, which was possible due to the reactivity of the phosphate group. Furthermore, using this method a variety of phosphate ester based CDs were synthesised and were found to show excellent molecular recognition in enantioselectivity of amino-acids.[14] This was hypothesised to be due to the stabilising interactions between the phosphate group of CD and the amino acid. Liu and co-workers also showed that by changing the phosphate ester side-arm, many tethered phosphorous compounds can be fine tuned to exhibit adapted chiral and molecular recognition abiltities.[15] In addition, mono-phosphates were also synthesised via polycondensation methods using 'green' sodium trimethyl phosphate.[16] This resulted in well-defined polymers that showed strong interactions with hosts and as complexing agents with such as Ca^{2+}. The group also showed the polymers strong affinity for porous hydroxyapatite, which led to poly-dispersed nanoparticles (50–150 nm) that could be used in bio-ceramics.

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Triphosphate functionalised CDs have also been successfully synthesised by using sodium cyclo-triphosphate[17] or other derivatives[18] but typically long reactions times are described.

Evidently, phosphate-based CDs represent a successful branch of carbohydrate chemistry and yet their bioisosteres have not been exploited. It has been well studied that phosphates are less stable than phosphonates, especially in biological mediums due to their susceptibility to various phosphatases and kinases. Thus, we decided to develop a new synthesis to access such phosphonate CDs that will provide an opportunity to broaden and enhance domains where phosphates have been already applied. This will especially provide a way to modulate biological molecular recognition and gain important insights into these mechanisms and pathways.

2. Results and discussion

Herein, we report for the first time a versatile methodology to prepare novel β-CDs bearing phosphonate moieties on the primary rim with high percentage yields. This new class of family has extensive applications as useful tools in biological systems as well as a key building block in complex CD chemistry.

We have synthesised CDs containing one or two phosphonate groups on the primary rim starting from native β-CD (Fig. 1). These new CD derivatives represent an extremely challenging task, due to the many hydroxyl groups present in CD and the lack of differentiation between them.

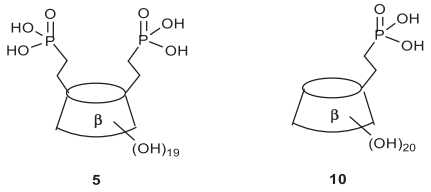

Fig. 1. Structure of A–D Di-**5** and Mono-**10** regioselectively functionalised phosphonic acid β-cyclodextrins.

Native CD was perbenzylated in preparation for the following regioselective deprotection, using a powerful strategy first introduced by A.J. Pearce and P. Sinay.[19] The reaction can remove one or two benzyl groups in a regioselective manner to obtain either the monol or A–D diol (transannular positioning on sugars A and D). The remarkable de-*O*-benzylation reaction typically proceeds in dry toluene and used a rather large excess of DIBAL as the reagent. However starting from the discovery of the blueprint strategy using simple carbohydrates,[20] and the evaluation of diethyleneglycol dibenzyl ether compounds, which confirmed the presence of two aluminium centred 'tweezers',[21] the group has skilfully optimised the protocol to limit the amount of DIBAL required.[22] Other groups have employed this original method with slight changes, which include; M. Bol's group[23] who added 4 Å molecular sieves and C.-C. Ling's group[24] who changed the reagent from DIBAL in toluene to DIBAL in hexane in order to gain more control over the reaction and thus obtain interesting tri- and tetra-deprotected derivatives. Nevertheless, other strategies exist to introduce the A–D functionality mainly by cleverly employing geometrically templated reagents, which was pioneered by I. Tabushi's group[25] and R. Breslow's group.[26]

In this synthesis, we have decided to use the method of Sinay whereby we achieved 55% A monol **6** and 70% A–D diol **1**, by changing the reaction conditions as previously described (Fig. 2). This specific regioselectivity can be determined by NMR, which allows a complete assignment of the diol by using ^{1}H and ^{13}C NMR signals and complementary 2D NMR experiments such as HSQC–TOCSY, ^{1}H–^{13}C and ROESY ^{1}H–^{1}H. Due to the complexity of the ^{1}H NMR spectra, not all the correlations with 2D-TOCSY ^{1}H–^{1}H can be fully identified. Thus, the use of ^{13}C characteristics allows us to gain important resolution of signals as no overlapping ^{13}C peaks of interest are observed. In this context, HSQC–TOCSY ^{1}H–^{13}C (mixing time of 240 ms, relaxation delay 2 s) with respect to CH_2 signals allows the identification of both complete spin systems for each glucose moiety containing a hydroxyl group, which appears at 2.60 ppm and 2.66 ppm. Each glucose moiety is then identified and completely assigned. ROESY ^{1}H–^{1}H confirms the regioselectivity of the molecule, by giving the correlation between H_1 (i) of one glucose moiety and H_4 (i+1) of the adjacent glucose moiety.

Initial attempts were carried out using classical methods based on the Michaelis–Arbuzov reaction to introduce the desired carbon–phosphorous bond starting from both bromo- and chloro-derivatives. Various reaction conditions were trailed including the type of trialkyl phosphite employed from triethyl phosphite to trimethylsilyl phosphite, the temperature, the reaction time and the solvent. However, after no significant results were observed, the adapted Michaelis–Becker reaction was investigated as an alternative route. Importantly, several bases were evaluated to remove the acidic proton from the dialkyl phosphite to allow the nucleophilic displacement to occur. Nevertheless, the key product was not obtained. As the goal of this work was to introduce phosphonate moieties directly onto the primary rim of β-CDs, the Horner–Wadsworth–Emmons (HWE) reaction was subsequently explored (Scheme 1).

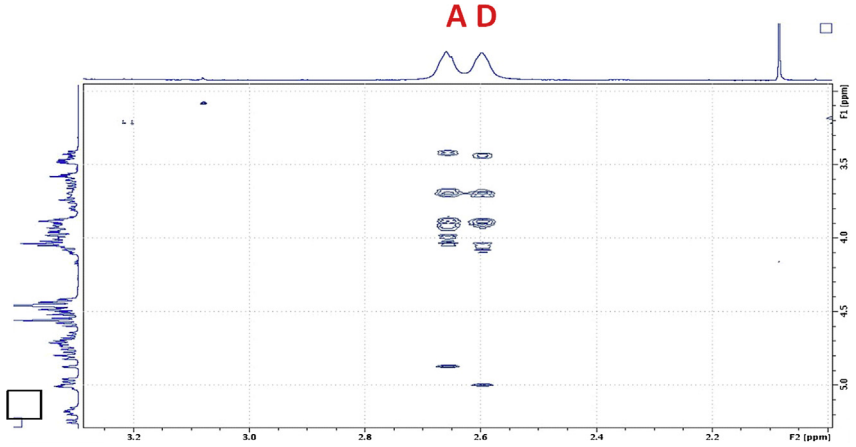

Fig. 2. 2D-TOCSY NMR ^{1}H–^{1}H (600 MHz) spectrum of compound **1** showing the two hydroxyl groups on position 6 confirming the A–D substitution pattern.