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Carbohydrate Research 342 (2007) 1989–1991
Carbohydrate RESEARCH

Rapid Communication

Per-*O*-(3-hydroxy)propyl-β-cyclodextrin: a cyclodextrin derivative bearing only primary hydroxyl groups

Nezha Badi* and Philippe Guégan*

Laboratoire Matériaux Polymères aux Interfaces-LRP, UMR CNRS 7581, Université d'Evry Val d'Essonne, Evry, France

Received 4 April 2007; received in revised form 6 June 2007; accepted 9 June 2007
Available online 16 June 2007

Abstract—Natural β-cyclodextrin (cyclomaltoheptaose) was treated with sodium hydride and allyl bromide to form the per-*O*-allyl-β-cyclodextrin. 9-BBN, sodium hydroxide and hydrogen peroxide were then added to form, after adequate treatments, the desired per-*O*-(3-hydroxy)propyl-β-cyclodextrin in yields close to 65%. This modified cyclodextrin, which bears only primary hydroxyl groups, can be used as a macro-initiator of the anionic polymerisation of ethylene oxide to form star-shaped polymers. The presence of only primary hydroxyl groups allows us to expect identical initiation kinetics for all the hydroxyl groups of the modified glucopyranosyl units.

Keywords: Cyclodextrin; Per-(3-hydroxypropyl)-β-cyclodextrin; Primary hydroxyl groups

Modified cyclodextrins (CDs) have been the object of many studies over the past 20 years.[1–4] CD derivatives are used in pharmacology,[5] the flavour industry,[6] etc. In these examples, their ability to form inclusion complexes is exploited. Despite elegant strategies to conduct to 'specific' modifications of CDs, work is still devoted to permodification of these cyclic compounds.[7] Indeed, a large amount of work is now devoted to the use of commercially available '(2-hydroxy)propyl cyclodextrins' (HP-CDs) in drug delivery.[8,9] Analyses of this compound show that its structure can vary from batch to batch[10] despite standardisation of the production of this compound by manufacturers. Statistical modification is inherent to this synthesis and variability in drug delivery can be encountered.

Other studies have reported the use of cyclodextrins as polymerisation initiators.[11–13] It is reported[7] that the primary hydroxyl group of the CD is often more nucleophilic than the two secondary hydroxyl functions (OH2 and OH3), which is a major drawback when initiation polymerisation is concerned. Indeed, considering these differences, we cannot envisage identical initiation kinetics of polymer growth at all positions of the CD. Topchieva et al.[11] have attempted anionic polymerisation of ethylene oxide using natural cyclodextrins as initiators. They have reported their doubts concerning the polymerisation initiated by the alcohol functionality at the 3-position, which contains a less reactive secondary hydroxyl group. To avoid such problems, a solution is the use of cyclodextrin derivatives bearing only primary hydroxyl groups. The synthesis of a cyclodextrins containing (3-hydroxy)propyl chains is preferable to the widely used (2-hydroxy)propyl cyclodextrin (HP-CD) (bearing secondary hydroxyl units) because of the better reactivity of primary hydroxyl groups.

In this paper we describe the synthesis of per-(3-hydroxy)propyl-β-cyclodextrin, a new molecule that can be used as a macro-initiator for the ethylene oxide anionic polymerisation. The aim of this work is not to substitute the hydroxyl groups of a CD by other functions but to try to make them of equal reactivity, more accessible and to some extent to increase the hydrophobic portion of the CD. These chemical modifications are necessary if one wants, for example, to use as initiators all the hydroxyl groups of the cyclodextrins.

* Corresponding authors. Tel.: +33 1 69 47 77 21; fax: +33 1 69 47 77 27 (P.G.); e-mail: pguegan@univ-evry.fr

0008-6215/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2007.06.013

In the synthesis of this compound, two strategies were explored. The first method, based on the work of Gnanou and co-wokers[14] on calixarenes is described in Scheme 1. With the procedure described in Scheme 1, we did not succeed in the complete modification of cyclodextrins by chloroethyl vinyl ether. The poor accessibility of the 3-hydroxyl group of the cyclodextrins might explain this unexpected result.

The desired product was then obtained using a second strategy (Scheme 2). The first step consists in forming the per-*O*-allyl-β-cyclodextrins by the addition of sodium hydride and allyl bromide to the unprotected cyclodextrins. This synthesis was previously described by Leydet et al.[15] with allyl iodide and led to yields ranging from 20% to 32%. Using the conditions we developed, the yields were close to 100%. In the second step, 9-borabicyclo[3.3.1]nonane (9-BBN), sodium hydroxide (NaOH) and hydrogen peroxide (H_2O_2) were added to form per-(3-hydroxy)propyl-β-cyclodextrins (65% yield). The hydroboration of alkenes using 9-BBN has been described in the literature by Brown and Chen[16] and, in the case of calixarenes, by Dondoni et al.[17]

A number of conditions were tested for carrying out the first alkylation reaction as shown in Table 1. When the reaction is carried out at 60 °C and a fourfold excess of sodium hydride and allyl bromide relative to each hydroxyl group are used, the yields are close to 100%.

Table 1. Conditions for obtaining per-*O*-allyl-β-cyclodextrin (**1**)

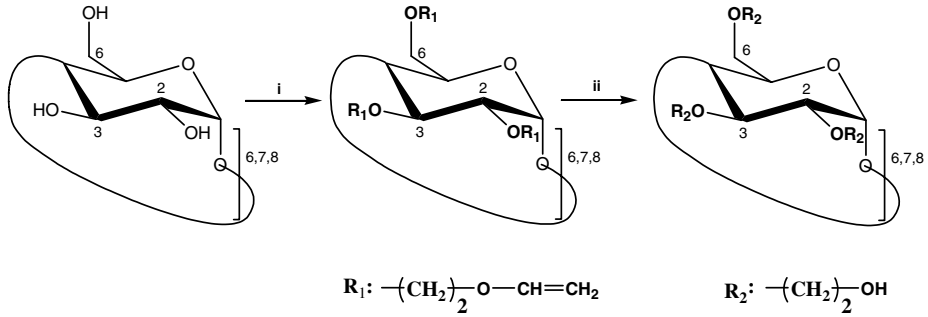
Exp.	[NaH]/[OH]	[Br_allyl]/[OH]	*T* (°C)	Reaction time with NaH	Reaction time with allylbromide (h)	Yields (%)
1	2	1.5	60	2 h 30 min	16	90
2	2	2	60	2 h 30 min	16	80
3	4	4	60	2 h 30 min	16	100

A general procedure is given in the Supplementary data. For the second step, an increase in reaction time with 9-BBN (Table 2) leads to an improvement of the yield.

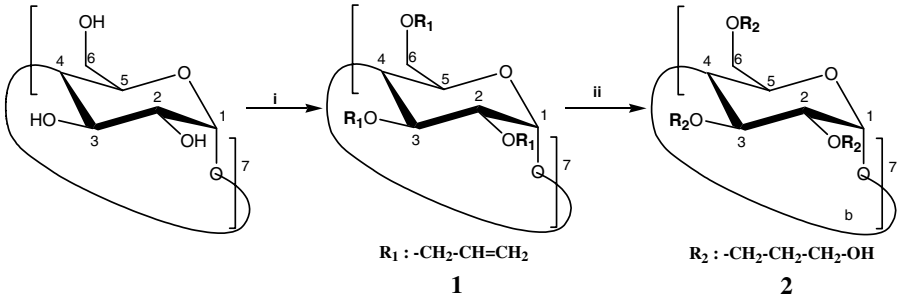
With this two step procedure, and after purification as described in the Supplementary data, a new kind of cyclodextrin was obtained in overall good yield (65%). The average degree of substitution was calculated from the signals in nuclear magnetic resonance spectra (see Supplementary data). The region at ~1.6 ppm, –(CH_2)– groups of hydroxypropyl chains, and the signals of anomeric protons at 5.1 ppm were compared to

Table 2. Formation of per-*O*-(3-hydroxy)propyl-β-cyclodextrin (**2**)

Exp.	[BBN]/[allyl]	[NaOH]/[allyl]	H_2O_2/[allyl]	Reaction with 9-BBN	Reaction with NaOH and H_2O_2	Yields
1	2	4	40	2 h at rt	4 h at 60 °C	50
2	2	4	40	4 h at rt	20 h at 60 °C	65



Scheme 1. Attempted strategy based on the work of Gnanou and co-workers.[14] Reagents and conditions: (i) Cs_2CO_3, DMF, 80 °C, chloroethyl vinyl ether, (ii) aqueous HCl, Et_2O/CH_2Cl_2 (4/1).



Scheme 2. Synthesis of per-*O*-(3-hydroxy)propyl-β-cyclodextrin. Reagents and conditions: (i) NaH, allyl bromide, DMF, 60 °C, (ii) 9-BBN, NaOH, H_2O_2, THF, 60 °C.

determine substitution. These NMR analyses allow us to conclude that all of the hydroxyl functions of the CD are modified. Mass spectrometry (electrospray ionisation) confirmed the purity of the product.

In conclusion, this paper has described the synthesis of a cyclodextrin derivative bearing only primary hydroxyl groups. The product per-*O*-(3-hydroxy)propyl-cyclodextrin is of particular interest as it possess both hydrophobic spacer chains (propyl) and hydrophilic primary hydroxyl groups. This new amphiphilic cyclodextrin can be used as an initiator of the ethylene oxide anionic polymerisation to obtain new star-shaped poly(ethylene oxide). The presence of only primary hydroxyl functions increases the reactivity and the accessibility of both the 2- and 3-positions of the CD. Therefore, identical initiation kinetics can be expected. This last assumption will be discussed in a further paper.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.06.013.

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