Carbohydrate Research 401 (2015) 58–63

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Regioselectivity in the formation of di- and tri-6-*O*-mesitylenesulfonates of α-cyclodextrin

Keisuke Yoshikiyo *, Misaki Shinjo, Yoshihisa Matsui, Tatsuyuki Yamamoto

Faculty of Life and Environmental Science, Shimane University, 1060 Nishikawatsu, Matsue, Shimane 690-8504, Japan

ARTICLE INFO

Article history:
Received 10 July 2014
Received in revised form 23 October 2014
Accepted 27 October 2014
Available online 8 November 2014

Keywords:
α-Cyclodextrin
Mesitylenesulfonylation
Regioselectivity
Regioisomers

ABSTRACT

The quantitative analysis of the reaction products for α-cyclodextrin (α-CD) with mesitylenesulfonyl chloride (MessCl) showed that di- and tri-mesitylenesulfonylation of the primary hydroxy groups of α-CD is regioselective. The reaction of mono-6-*O*-mesitylenesulfonyl-α-CD with MessCl in pyridine gave less $6^A,6^C$-di-*O*-mesitylenesulfonyl-α-CD than $6^A,6^B$-di-*O*-mesitylenesulfonyl-α-CD. The reaction of $6^A,6^D$-di-*O*-mesitylenesulfonyl-α-CD with MessCl gave less $6^A,6^B,6^E$-tri-*O*-mesitylenesulfonyl-α-CD than $6^A,6^B,6^D$-tri-*O*-mesitylenesulfonyl-α-CD. These results indicate that the mesitylenesulfonyl group attached to glucopyranose-A (Glc-A) retards further mesitylenesulfonylation of the primary hydroxy group of Glc-C. The ^{1}H NMR spectra of these modified α-CDs showed that the signal for the primary hydroxy and anomeric protons of Glc-C are significantly shifted upfield by the mesitylenesulfonyl group of Glc-A.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6–8 glucopyranoses (Glc) linked via α-1,4 glycosidic bonds, having hydrophobic cavities at the center of the molecules, in which guests, molecules or ions, are selectively included to form inclusion complexes. Owing to the guest selectivity, CDs have long been studied as model compounds for biological receptors[1,2] or artificial molecular recognition tools.[3–5] Especially, the chemically modified CDs have attracted considerable attention, as the modifications of functional groups on CDs often result in the expression of unprecedented functions such as a stronger guest binding comparable to the biological systems, or enhanced chiral recognition ability, etc.[6,7] Most of the CD derivatives are synthesized via activated compounds in which CD hydroxy groups are substituted with good leaving groups. Among them, the sulfonyl group is one of the most excellent leaving groups, with high reactivity to nucleophiles. The sulfonylation of hydroxy groups of CDs with *p*-toluenesulfonyl chloride is frequently used for this purpose. However, the reaction is nonselective and often produces a mixture of the toluenesulfonylated products both at the primary as well as the secondary side, together with di- and tri-substituted derivatives.[8] The sulfonylation of CD using mesitylenesulfonyl chloride (MessCl) was reported to be an efficient method for a selective sulfonylation of the primary hydroxy groups, C(6)-OHs, and gives a mixture of mono- and poly-6-*O*-sulfonylated derivatives.[9] As illustrated in Scheme 1, di-6-*O*-mesitylenesulfonylated α-CD, α-CD(Mess)$_2$, has three regioisomers such as $6^A,6^B$-, $6^A,6^C$-, and $6^A,6^D$-di-*O*-mesitylenesulfonyl-α-CDs (AB-, AC-, and AD-isomers, respectively), and tri-6-*O*-mesitylenesulfonylated α-CD, α-CD(Mess)$_3$, has four regioisomers such as $6^A,6^B,6^C$-, $6^A,6^B,6^D$-, $6^A,6^B,6^E$-, and $6^A,6^C,6^E$-tri-*O*-mesitylenesulfonyl-α-CDs (ABC-, ABD-, ABE-, and ACE-isomers, respectively). These regioisomers have successfully been separated and identified.[10–13] However, not much has been reported on the quantitative analysis on the formation ratio of regioisomers of α-CD(Mess)$_2$ and α-CD(Mess)$_3$, except for the works by Fujita et al. which reported yield of three regioisomers of α-CD(Mess)$_2$.[10,11]

From the results of our recent experiments, we also found that AC-isomer, one of the three regioisomers of α-CD(Mess)$_2$, was formed in about half the yield of AB-isomer in the reaction of α-CD with MessCl in pyridine. If this mesitylenesulfonylation reaction has no regioselectivity, AB- and AC-isomers would be formed in the same yield. The apparent difference in yield between these isomers indicates that the reaction is regioselective. This finding had led us to investigate these reactions in detail.

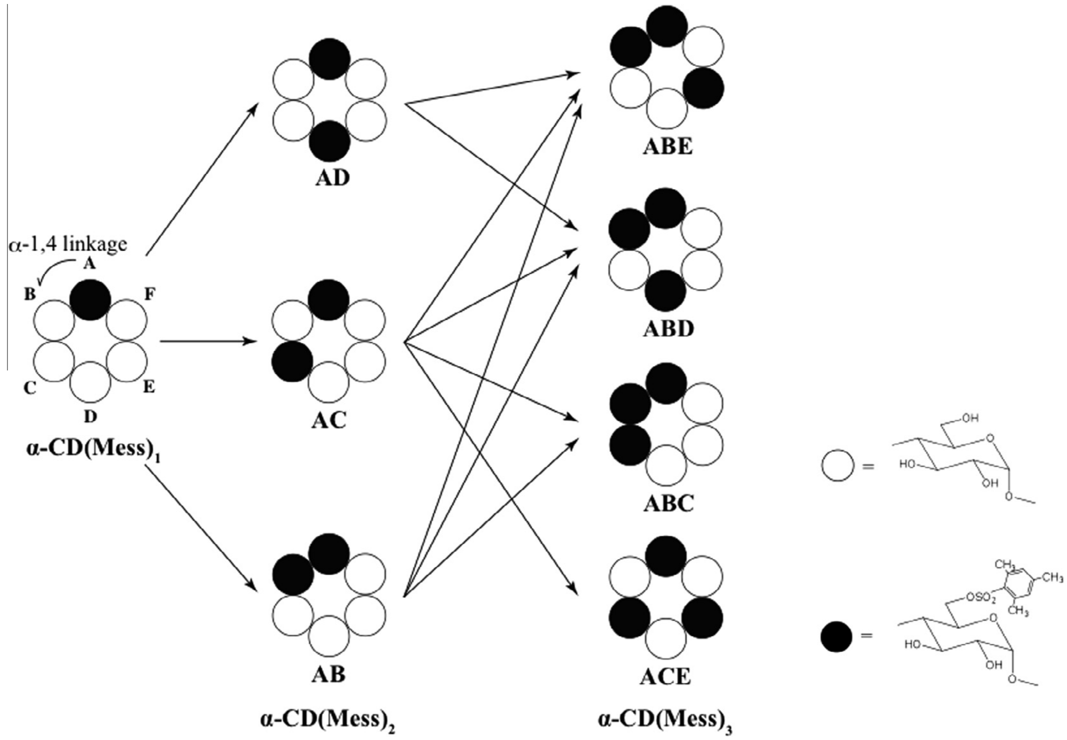
2. Results and discussions

Dried α-CD was allowed to react with MessCl in pyridine at 2 °C, and aliquots were withdrawn at hourly intervals. The concentrations of the reaction products in the aliquots were determined by means of UFLC (ultra-fast liquid chromatography) as described in

---

* Corresponding author.
E-mail address: yoshikiyo@life.shimane-u.ac.jp (K. Yoshikiyo).

http://dx.doi.org/10.1016/j.carres.2014.10.027



Scheme 1. Mesitylenesulfonates of α-CD examined in the present study and formation pathways. Letters A–F represent the Glc residues when viewed from the primary hydroxy side.

the Experimental. The concentrations of mono-6-*O*-mesitylenesulfonyl-α-CD, α-CD(Mess)$_1$, and three regioisomers of α-CD(Mess)$_2$ formed are plotted versus the reaction time in Figure 1. α-CD(Mess)$_1$ was smoothly produced after the reaction started (left scale), together with three regioisomers of α-CD(Mess)$_2$ with lower concentrations (right scale) than the α-CD(Mess)$_1$. The concentrations of α-CD(Mess)$_2$ were low at the beginning of the reaction and gradually increased with time, suggesting that α-CD(Mess)$_2$ is formed by the sulfonylation of the formerly produced α-CD(Mess)$_1$. If the C(6)-OH of each Glc of the α-CD(Mess)$_1$ has the same reactivity with MessCl, then AB- and AC-isomers would be produced in an equal concentration, and in twice of AD-isomer; (AB/AC/AD = 1:1:0.5). However, the molar ratio of the products was about 1.00:0.55:0.45 (AB/AC/AD) in every aliquot, showing that the AC-isomer was produced considerably less than AB-isomer. A similar result has been reported, in which the molar ratio of the product was 1.00:0.67:0.54 (AB/AC/AD).[10,11] The results clearly show that the second Mess group is introduced into the α-CD(Mess)$_1$ with regioselectivity.

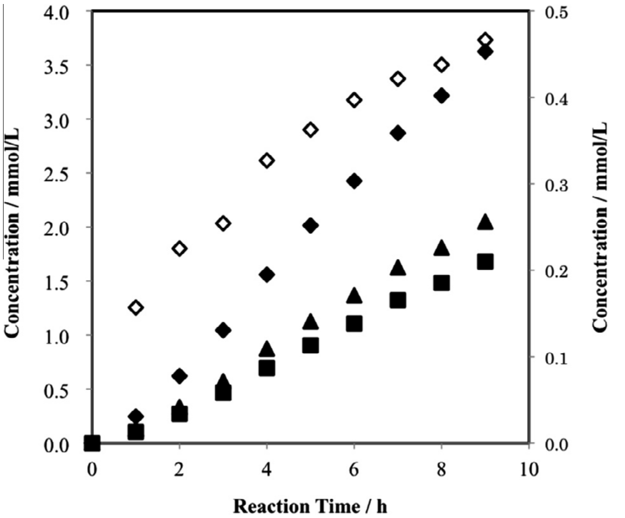


Figure 1. Plots of the concentration of α-CD(Mess)$_1$ (◇), left axis, and AB-(◆), AC-(▲), and AD-isomers (■), right axis, versus the reaction time for the reaction of α-CD with MessCl in pyridine at 2 °C. Average molar ratio of AB/AC/AD was 1.00:0.55 ± 0.01:0.45 ± 0.01.

In order to investigate the formation of α-CD(Mess)$_2$ in more detail, α-CD(Mess)$_1$ was directly mesitylenesulfonylated in pyridine to form α-CD(Mess)$_2$. The time-dependent changes in the concentration of three regioisomers of α-CD(Mess)$_2$ are shown in Figure 2. The result showed that the molar ratio of AB/AC/AD = 1.00:0.57:0.44, virtually the same as the direct reaction of α-CD as a reactant. The total amount of four isomers of α-CD(Mess)$_3$ in the crude product was also determined to be less than 4% of α-CD(Mess)$_2$. This shows that further sulfonylation of α-CD(Mess)$_2$ to α-CD(Mess)$_3$ did not practically affect the molar ratio of α-CD(Mess)$_2$. AC-isomer is formed from α-CD(Mess)$_1$ when C(6)-OH of either Glc-C or -E is sulfonylated. Glc-C is the second adjacent Glc in a counter-clockwise direction from Glc-A, and Glc-E is the second adjacent Glc in a clockwise direction. The small molar ratio of AC-isomer to AB-isomer shows that C(6)-OHs of Glc-C and/or Glc-E in α-CD(Mess)$_1$ were less reactive than the others.

Then, we carried out experiments using AD-isomer as a reactant to investigate which of the C(6)-OH of Glc-C or -E is more restricted in the sulfonylation. If the Mess groups of Glc-A and -D of the AD-isomer retard the sulfonylation of the C(6)-OH of the second adjacent Glc in a counter-clockwise direction (Glc-C and -F), ABE-isomer would be a minor product, and ABD-isomer, a major one. On the contrary, if they retard the sulfonylation of the C(6)-OH of the second adjacent Glc in a clockwise direction (Glc-E and -B), ABD-isomer would be a minor, and ABE-isomer, a major product. The quantitative analysis of the product in this reaction