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Selective Transport of Saccharides Through a Liquid Membrane Using Cyclodextrin Dimer

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Abstract

A new effective transport system for saccharides through a liquid membrane was constructed. The transport rate of D-ribose in the condition of the liquid membrane with cyclodextrin dimer (**2**) as a transporter is 2.5 timer larger than that without the transporter, whereas the transport rate of D-ribose in the condition of the liquid membrane with cyclodextrin monomer (**1**) is almost the same as that without the transporter. The transport rate of methyl D-glucoside by **2** is over twice than that by **1**. The transport rate of D-deoxyribose by **2** is larger than that by **1**.

Introduction

Recently, much effort has been devoted to the construction of the systems for selective transport of saccharides through a liquid membrane containing of artificial transporters, because such system is useful not only for separation of a mixture of saccharides but for clarifying the mechanism of action of saccharide transport through a biomembrane [1–4]. The separation of a mixture of saccharides is not easy, because most saccharides are isomers that only differ in the configuration of specific hydroxyl groups. One of effective methods for separation of a mixture of saccharides is the use of transport through the selective membrane containing the transporter that can selectively bind a saccharide. Most successful transporter binds with saccharide through the selective formation of hydrogen bonds or covalent bonds. The transport rate of the saccharide through a hydrophobic liquid membrane is quite slow, because the saccharide is a hydrophilic compound. The transport rate of the saccharide through the liquid membrane would increase, if the saccharide could be cover up by a hydrophobic shell that has functional groups to interact with the hydroxyl groups of the saccharide on the inside of the shell. Phenylboronic acid derivatives, reversed micelles, and lipophilic alkaline earth metal complexes were used for the transporter for the saccharide [1–4]. It is reported that a ternary complex of saccharide, water and resorcinarene is effective for the selective transport of the saccharide [5]. Cyclodextrins (CDs) are cyclic oligosaccharides composed of six, seven, eight or more glucose units [6–8]. Because CD has many hydroxyl groups and the secondary hydroxyl groups are aligned on the coplanar, a CD dimer would be a powerful transporter for saccharides, if the CD dimer can wrap saccharides with hydrogen bonds by the hydroxy groups of CD at the secondary hydroxyl side and the primary side of CD was changed to be hydrophobic by chemical modification. In this paper, we report a new excellent transport system for saccharides through a liquid membrane using a cyclodextrin dimer.

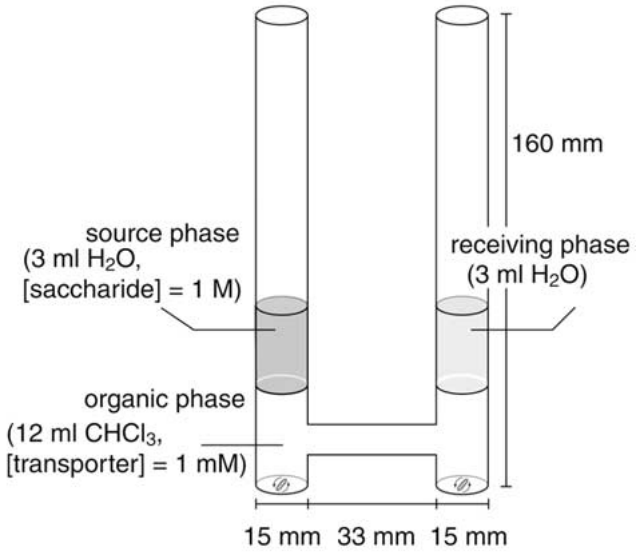

Figure 1. U-type glass cell for the transport experiments.

Experimental

Material

Synthesis of 1

A solution of *tert*-butyldimethylchlorosilane (14.5 g) in pyridine (150 ml) was added to a solution of β-cyclodextrin

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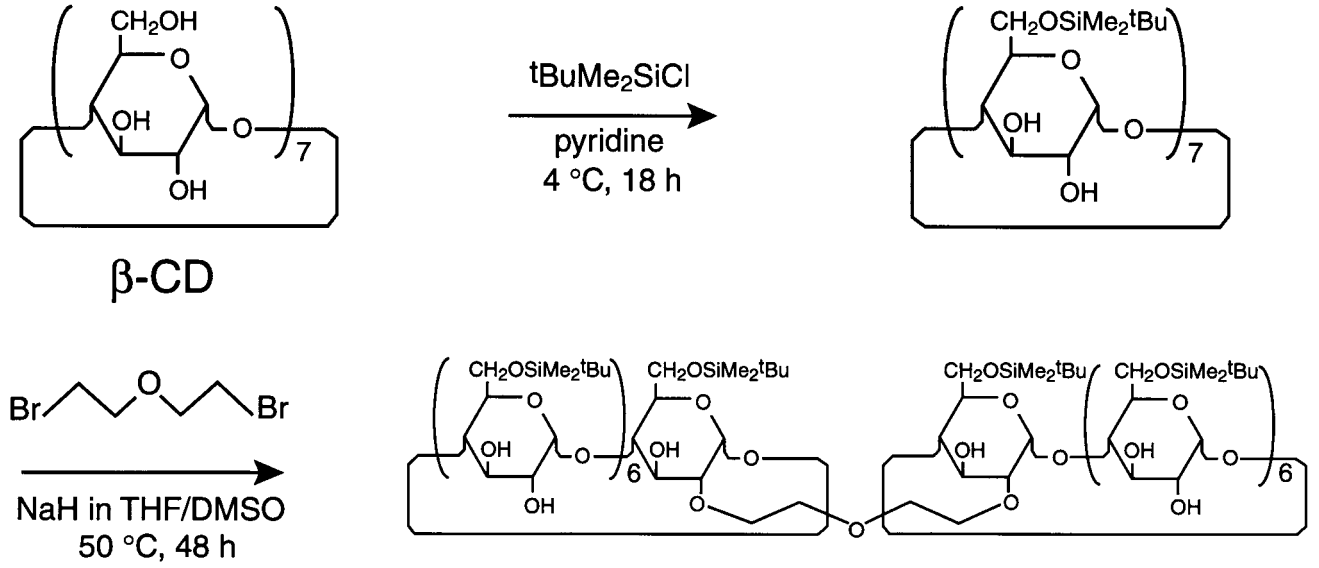

Scheme 1.

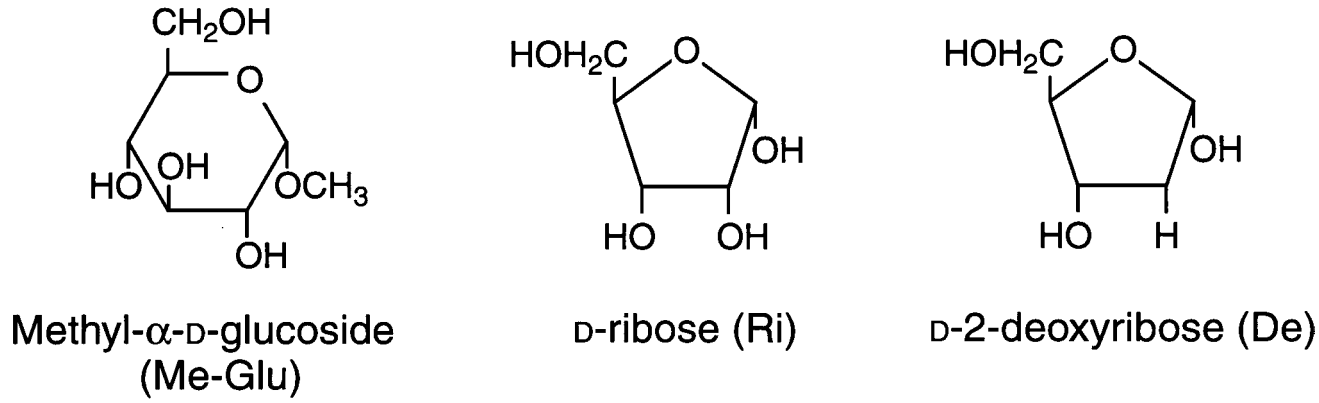

Figure 2. The substrates of the transport experiments.

(9 g) in pyridine (100 ml) for 3.5 h at 0 °C under nitrogen. The reaction mixture was stirred for 18 h at room temperature under nitrogen. After removal of the solvent, the residue was dissolved in chloroform, washed with 1N hydrochloric acid aqueous solution, saturated aqueous solution of sodium hydrogen carbonate, and saturated brine, and dried over magnesium sulfate. The crude product was purified by column chromatography on silica gel (chloroform : ethyl acetate = 7 : 0.1) and by recrystallization from methanol/chloroform. The product was identified by elemental analysis, some kinds of ^{1}H-NMR spectra including 2D NMR, and mass spectrum.

Synthesis of 2

NaH (18 mg) was added to a solution of **1** (1.0 g) in mixed solvent of THF (30 ml) and DMSO (3 ml) and the mixture was stirred at room temperature. To this mixture was added a solution of bis(2-bromoethyl) ether (57 mg) in THF (20 ml) for 10 h at 50 °C. After removal of the solvents, the residue was dissolved in chloroform, washed with saturated aqueous solution of ammonium chloride and dried over magnesium sulfate. The crude product was purified by column chromatography on silica gel (chloroform : methanol : water = 5 : 1 : 0.1). The fractions containing the desired product were concentrated under reduced pressure to give a white powder (yield 10.9%). The product was identified by elemental analysis, some kinds of ^{1}H-NMR spectra including 2D NMR, and mass spectrum.

Methods

The transport experiment was performed with a U-tube glass cell across a chloroform liquid membrane from an aqueous source phase containing a saccharide to an aqueous receiving phase (Figure 1). Three conditions were examined for each saccharide; the chloroform liquid membrane in the presence of **1** or **2**, and in the absence of them. A small amount of the aqueous receiving phase was sampled, suitably diluted, and assayed by HPLC at constant intervals. Tosoh TSKgel Amide-80 was used for a column of HPLC. Saccharides were detected by a refractive index meter.

Results and discussion

A new transporter was prepared as shown in Scheme 1. All the primary hydroxyl groups of CD were protected with *tert*-

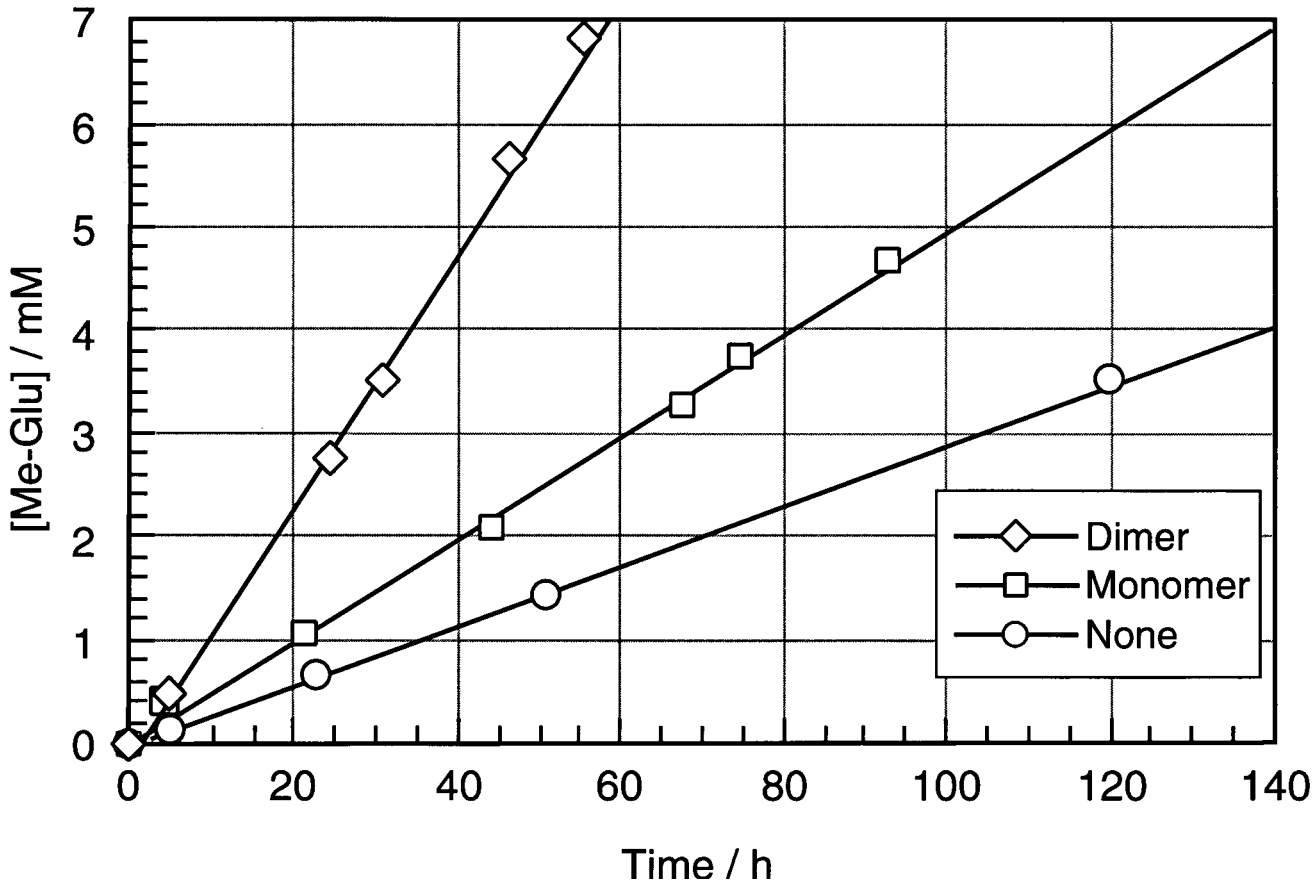

Figure 3. Time course of the concentration of methyl-α-D-glucoside in receiving phase. Source phase (3 ml H_2O, [Me-glu] = 1.0 M); organic phase (12 ml $CHCl_3$, [Monomer] = [Dimer] = 1.0 mM); receiving phase (3 ml H_2O), 25 °C.

buthyldimethlylsilyl groups in order to change the primary hydroxyl side of CD to be hydrophobic [9–10]. The silylated CD **1** was insoluble in water but was soluble in chloroform. Two heptakis(6-*O*-tert-butyldimethylsilyl)-β-CD (**1**) were linked with bis(bromoethyl) ether to obtain the cyclodextrin dimer **2** in a 10% yield. After purification by column chromatography, the product was identified by elemental analysis, some kinds of ^{1}H-NMR spectra including 2D NMR, and mass spectrum.

The transport experiments were performed with a U-tube glass cell across a chloroform liquid membrane from an aqueous source phase containing a saccharide to an aqueous receiving phase (Figure 1). The three kinds of conditions for the liquid membrane were examined; the chloroform liquid membrane contains in the presence of **1** or **2**, and in the absence of them. Three kinds of saccharides were used for the substrates of the transport experiments; methyl-α-D-glucoside, D-ribose, and D-2-deoxyribose (Figure 2).

The amount of transported saccharide to the receiving phase increased linearly with time in the all cases (Figure 3). The transport rate was determined by the slope of this time course of the amount of the transported saccharide (Figure 4). The transport rate of D-ribose in the condition of the liquid membrane in the presence of the CD dimer **2** is 2.5 timers larger than that in the absence of the transporter, whereas the transport rate of D-ribose in the condition of the liquid membrane in the presence of the CD monomer **1** is almost the same as that in the absence of the transporter. The transport rate of methyl D-glucoside by **2** is over twice than that by **1**. Because D-deoxyribose is more hydrophilic than the other saccharides and its transport rate in the absence of the transporter is fast, the difference of the rates among the three kinds of conditions is small but the transport rate of D-deoxyribose by **2** is larger than that by **1**. These experimental results indicate that **2** is quite effective for the transporter in the liquid membrane to transport saccharides. The CD dimer **2** can wrap the saccharides but the CD monomer **1** is not enough to wrap the saccharides. Two CD monomer **1** could make complex with a saccharide such as the CD dimer but the amount of this complex would be quite small. Therefore, the CD dimer is more effective for the transport of the saccharide through the liquid membrane than CD monomer. If functional groups that selectively interact with the hydroxyl groups of the saccharide will be introduced to the secondary hydroxyl side of CD, more successful transporter will be constructed.

Conclusion

A new effective transport system for saccharides through a liquid membrane was constructed using the CD dimer as a transporter. This system is more successful for the trans-

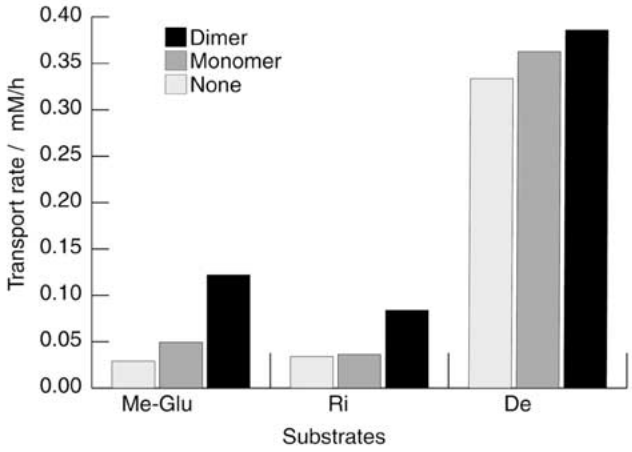

Figure 4. Transport rates of monosaccharides through a liquid membrane mediated by cyclodextrin derivatives.

port of the saccharide through the liquid membrane than the system using the CD monomer.

Acknowledgments

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References

1. T. Araki and H. Tsukube: *Liquid Membranes: Chemical Applications*, CRC Press, Florida (1990).
2. N. Tbeur, T. Rhlalou, M. Hlaïbi, D. Langevin, M. Métayer, and J-F. Verchère: *Carbohydr. Res.* **329**, 409 (2000).
3. K. Kasuga, T. Hirose, S. Aiba, T. Takahashi, and K. Hiratani: *Tetrahedron Lett.* **39**, 9699 (1998).
4. T. Kida, D. Furue, A. Masuyama, Y. Nakatsuji, and I. Ikeda: *Chem. Lett.* 1996, 733.
5. Y. Aoyama, Y. Tanaka, and S. Sugahara: *J. Am. Chem. Soc.* **111**, 5397 (1989).
6. J. Szejtli and T. Osa (eds.): *Comprehensive Supramolecular Chemistry*, Vol. 3., Pergmon, Oxford (1996).
7. J. Szejtli: *Cyclodextrin Technology*, Kluwer, Dordrecht (1998).
8. G. Wenz: *Angew. Chem., Int. Ed. Engl.* **33**, 803 (1994).
9. D. Alker, P.R. Ashton, V.D. Harding, R. Königer, J.F. Stoddart, A.J.P. White, and D.J. Williams: *Tetrahedron Lett.* **35**, 9091 (1994).
10. M.R. de Jong, J.F.J. Engbersen, J. Huskens, and D.N. Reinhoudt: *Chem. Eur. J.* **6**, 4034 (2000).