Amphiphilic Cyclodextrins as Novel Monosaccharide Transport Carriers through a Bulk Liquid Membrane

Toshiyuki Kida, Takeru Ohe, Hiroyuki Higashimoto, Hitoshi Harada, Yohji Nakatsuji, Isao Ikeda, and Mitsuru Akashi*

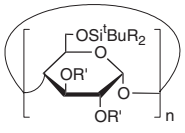
Department of Molecular Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871

(Received November 18, 2003; CL-031112)

Monosaccharides, such as D-ribose, D-xylose, and D-glucose, were successfully transported through a bulk liquid membrane by using amphiphilic cyclodextrin carriers. The transport ability was remarkably affected by the lipophilicity and ring size of the carrier molecule.

The development of a saccharide transport system through a liquid membrane by artificial carriers has attracted much attention. A saccharide transport system is potentially useful as a tool for saccharide separation and as a model for studying the function of saccharide transporters in biological membranes. Thus far, most of the saccharide transport systems have been constructed with boronic acid derivatives, which covalently complex saccharide diols to yield cyclic boronate esters, as carriers.[1] On the other hand, there have been only a few saccharide transport systems reported using noncovalent interactions, such as hydrogen bonding and ion–dipole interactions, between the carrier and the guest saccharide,[2] although noncovalent interactions play a crucial role in the biological carbohydrate recognition.

Cyclodextrins (CDs) are α-(1,4)-linked cyclic oligosaccharides usually consisting of 6, 7, or 8 glucopyranose units and have multiple and convergent hydroxyl groups on their secondary and primary faces. Molecular modeling studies show that the hydroxy groups on the secondary face of CD, especially those of β-CD, are situated in positions that permit multiple hydrogen bonding to the hydroxy groups of monosaccharides such as D-xylopyranose and D-glucopyranose. Therefore, an amphiphilic CD obtained by lipophilic modification of the primary face of CD, bearing free hydroxy groups on the secondary face, can be expected to function as a saccharide transport carrier via multiple hydrogen bonds. In this letter, we report monosaccharide transport through a bulk liquid membrane by use of an amphiphilic CD as a novel carrier.



1a: R = Ph, R' = H, n = 6 **2a**: R = Me, R' = H, n = 6
1b: R = Ph, R' = H, n = 7 **2b**: R = Me, R' = H, n = 7
1c: R = Ph, R' = H, n = 8 **2c**: R = Me, R' = H, n = 8
1d: R = Ph, R' = Me, n = 7

Figure 1. Structures of amphiphilic cyclodextrin carriers.

Per(6-*O*-*tert*-butyldiphenylsilyl)CDs **1a–c** and per(6-*O*-*tert*-butyldimethylsilyl)CDs **2a–c** were chosen as amphiphilic CD carriers (Figure 1). These compounds were prepared according to the previously reported method.[3] The CD derivatives are hardly soluble in water but have good solubility in chloroform as a liquid membrane. D-Ribose, D-xylose, and D-glucose were employed as guest monosaccharides. Transport experiments were carried out using a U-tube apparatus (1.5-cm internal diameter, 14.6-cm high, 2-cm distance between the two arms) equipped with a stirring rod and magnetic stirrer (300 rpm) at 25 °C. A chloroform solution (15 mL) containing an amphiphilic CD was placed in the bottom of the tube, and two portions of aqueous solutions (both 3 mL) were carefully added on top of the chloroform solution. The details of transport conditions are summarized in the footnotes to Table 1. The saccharide concentrations in the receiving phase were determined by HPLC (Shodex NH2P-50 column, 4.6 mm internal diameter $\times$250 mm, acetonitrile/water = 75/25 (v/v) as an eluent) using ethylene glycol as an internal standard. Each experiment was repeated at least three times to ensure reproducibility ($\pm$10%).

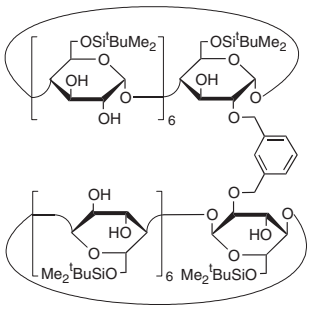
Table 1. Transport rates of D-ribose, D-xylose, and D-glucose using amphiphilic cyclodextrin carriers

Carrier	Transport rate[a]/10^{-8} mol h^{-1}		
	D-Ribose[b]	D-Xylose	D-Glucose
1a	13	≈0	≈0
1b	220	133	30
1c	209	120	34
1d	≈0	≈0	≈0
2a	10	≈0	≈0
2b	50	13	3
2c	47	15	≈0
3	112	64	12

[a] Transport conditions: source phase (H_2O, 3 mL, [D-ribose] = [D-xylose] = [D-glucose] = 1.5 mol dm^{-3}); organic phase ($CHCl_3$, 15 mL, [carrier] = 1.0×10^{-2} mol dm^{-3} except for **3** whose concentration is 5.0×10^{-3} mol dm^{-3}); receiving phase (H_2O, 3 mL), 25 °C, 48 h, 300 rpm.
[b] Transport rates of D-ribose were corrected by subtracting its leakage rate (2.0×10^{-7} mol h^{-1}) in the absence of a carrier.

Table 1 shows the results of competitive transport toward D-ribose, D-xylose, and D-glucose using amphiphilic CD carriers. Leakage of D-ribose from the source to the receiving phase was observed in the absence of a carrier, and the transport rate of D-ribose was corrected by subtracting its leakage rate (2.0×10^{-7} mol h^{-1}). Heptakis(6-*O*-*tert*-butyldiphenylsilyl)-β-CD **1b** and octakis(6-*O*-*tert*-butyldiphenylsilyl)-γ-CD **1c** showed the highest transport ability toward these monosaccharides among the carriers examined in this work. In these cases, the transport rate of the guest monosaccharide increased in the order of D-glu-

cose < D-xylose < D-ribose. This order is consistent with the increasing order of lipophilicity of the saccharide molecule,[4] suggesting that guest lipophilicity affects transport rates, similar to the previously reported saccharide transport system using reversed micelle carriers.[5] In contrast, the corresponding α-CD derivative **1a** showed much lower transport ability, hardly transporting D-xylose and D-glucose. These results indicate that the ring size of the parent CD remarkably affects the transport ability of per(6-*O*-*tert*-butyldiphenylsilyl)CDs. Ring-size effects were also observed in the per(6-*O*-*tert*-butyldimethylsilyl)CD series **2a–c**, though replacement of the diphenyl substituents on the silicon atom to dimethyl groups largely decreased the transport ability, possibly due to a decrease in the lipophilicity of the carrier molecule leading to a decrease in the solubility of the carrier-guest complex in the liquid membrane. Methylation of all the hydroxy groups of **1b** drastically decreased the saccharide transport ability, suggesting that hydrogen bonding interaction between the hydroxy groups of **1b** and those of the guest monosaccharides is responsible for the present carrier-guest complexation.



3

Figure 2. Structure of amphiphilic β-CD dimer **3**.

Apparent aggregation number measurements by vapor pressure osmometry (VPO) for the carriers **1a–d** and **2a–c** (1.0×10^{-2} mol dm^{-3}) in chloroform, which contains almost the same amount of water (930 ± 20 ppm) as in the liquid membrane during the transport experiments, show that the carrier molecules **1a–c** and **2a–c** tend to dimerize in the liquid membrane; on the other hand, carrier **1d**, which does not bear free hydroxy groups, exists as a monomer.[6] Aoyama et al. reported that extraction of methyl β-D-glucopyranoside from water into chloroform by using amphiphilic resorcinol cyclotetramer as a host molecule occurs through the formation of a sandwich-like 2:1 host–guest complex; the guest saccharide is encapsulated by two host molecules so that guest hydroxy groups are not exposed to the surrounding lipophilic media, which would occur in a 1:1 complex.[7] Thus, it is reasonable to assume that in the present transport system, the guest monosaccharides are mainly transported through sandwiching by two amphiphilic cyclodextrin molecules in the liquid membrane. To support this assumption, we prepared amphiphilic β-CD dimer **3** (Figure 2) by the reaction of two equivalents of heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD **2b** with α,α'-dibromo-*m*-xylene in the presence of sodium hydride as a base in THF.[8] The dimer **3** exhibited higher transport ability toward these monosaccharides than the corresponding monomer **2b** even at half-concentration (5.0×10^{-3} mol dm^{-3}). This finding clearly shows that the transport of the monosaccharides is effectively carried out through sandwiching of the guest molecule by two CD rings in the liquid membrane. The much lower transport ability of α-CD derivatives **1a** and **2a** may be explained by considering that these carriers can not form enough lipophilic sandwich-like complexes with guest monosaccharides, especially D-xylose and D-glucose, to be solubilized into the liquid membrane; **1a** and **2a** do not have sufficiently large rings to completely encapsulate these guests by sandwiching. At present, the detailed structure of the carrier-guest complex in the liquid membrane is not clear.

In conclusion, the transport of monosaccharides through a bulk liquid membrane was successfully carried out by using amphiphilic β- and γ-CD carriers. The transport ability was affected by the lipophilicity and ring size of the carrier molecules, implying that the lipophilicity of carrier–guest complexes is closely related to the transport ability. A detailed mechanistic study of saccharide transport using the CD carriers and the optimization of transport conditions are now in progress in our laboratory.

References and Notes

1 T. Shinbo, K. Nishimura, T. Yamaguchi, and M. Sugiura, *J. Chem. Soc., Chem. Commun.*, **1986**, 349; B. F. Grotjohn and A. W. Czarnick, *Tetrahedron Lett.*, **30**, 2325 (1989); L. K. Mohler and A. W. Czarnik, *J. Am. Chem. Soc.*, **115**, 2998 (1993); M.-F. Paugam and B. D. Smith, *Tetrahedron Lett.*, **34**, 3723 (1993); M.-F. Paugam, G. T. Morin, and B. D. Smith, *Tetrahedron Lett.*, **34**, 7841 (1993); G. T. Morin, M.-F. Paugam, M. P. Hughes, and B. D. Smith, *J. Org. Chem.*, **59**, 2724 (1994); G. T. Morin, M. P. Hughes, M.-F. Paugam, and B. D. Smith, *J. Am. Chem. Soc.*, **116**, 8895 (1994); E. Lambert, E. C. Breinlinger, and V. M. Rotello, *J. Org. Chem.*, **60**, 2646 (1995); J. A. Riggs, R. K. Litchfield, and B. D. Smith, *J. Org. Chem.*, **61**, 1148 (1996); M. Di Luccio, B. D. Smith, T. Kida, C. P. Borges, and T. L. M. Alves, *J. Membr. Sci.*, **174**, 217 (2000).

2 J. A. Riggs and B. D. Smith, *J. Am. Chem. Soc.*, **119**, 2765 (1997); K. Kasuga, T. Hirose, S. Aiba, T. Takahashi, and K. Hiratani, *Tetrahedron Lett.*, **39**, 9699 (1998); N. Tbeur, T. Rhlalou, M. Hlaïbi, D. Langevin, M. Métayer, and J.-F. Verchère, *Carbohydr. Res.*, **329**, 409 (2000).

3 R. F. Cunico and L. Bedell, *J. Org. Chem.*, **45**, 4797 (1980); P. Fügedi, *Carbohydr. Res.*, **192**, 366 (1989).

4 K. Miyajima, K. Machida, and M. Nakagaki, *Bull. Chem. Soc. Jpn.*, **58**, 2595 (1985); M. Janado and Y. Yano, *J. Solution Chem.*, **14**, 891 (1985).

5 T. Kida, D. Furue, A. Masuyama, Y. Nakatsuji, and I. Ikeda, *Chem. Lett.*, **1996**, 733.

6 Apparent aggregation numbers of **1a–d** and **2a–c** in chloroform containing water of 930 ± 20 ppm at 30 °C are as follows: **1a** = 1.6, **1b** = 1.7, **1c** = 1.6, **1d** = 1.0, **2a** = 1.9, **2b** = 1.9, **2c** = 1.8.

7 Y. Kikuchi, Y. Tanaka, S. Sutarto, K. Kobayashi, H. Toi, and Y. Aoyama, *J. Am. Chem. Soc.*, **114**, 10302 (1992).

8 Spectroscopic data for compound **3**: ^{1}H NMR(400 MHz, $CDCl_3$) δ −0.04–0.07 (m, 84H), 0.69–1.00 (m, 126H), 3.29–4.34 (m, 88H), 4.57–4.96 (m, 14H), 5.07–5.58 (m, 14H), 6.09–6.77 (m, 12H), 6.97–7.51 (m, 4H); MALDI–TOF *m*/*z*: 3995 ($M + Na^+$), 4011 ($M + K^+$); Anal. Calcd for $C_{176}H_{342}O_{70}Si_{14}\cdot 3H_2O$: C, 52.51; H, 8.71. Found: C, 52.20; H, 8.48%.

Published on the web (Advance View) February 2, 2004; DOI 10.1246/cl.2004.258