Pergamon

Tetrahedron Letters 39 (1998) 9699–9702

TETRAHEDRON
LETTERS

Transport of Monosaccharides through a Liquid Membrane Mediated by Lipophilic Alkaline Earth Metal Complexes

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Received 3 September 1998; revised 14 October 1998; accepted 16 October 1998

Abstract

Lipophilic alkaline earth metal complexes, prepared from the corresponding metal hydroxides and phosphoric acid diesters, are quite effective for the transport of some monosaccharides, especially ribose, across a chloroform liquid membrane under neutral conditions.

Keywords: Carbohydrates; Complexes; Host compounds; Molecular recognition.

Considerable attention has been focused on the extraction [1] and transport [2] of saccharides into or through organic phases by synthetic receptors. Most of these receptors bind with saccharides through the formation of hydrogen bonds or covalent bonds. Utilization of metal coordination offers an alternative way to design new receptors for saccharides, though the examples are few [3]. It has been known that some metal cations, especially alkaline earth and lanthanide metal ions make complexes with saccharides in water even under neutral conditions [4]. Furthermore, in nature, interactions between alkaline earth metal cations, especially calcium ion, and saccharides are involved in some important biological processes [5] such as calcium-dependent cell-cell interactions [6] and calcium-mediated carbohydrate-protein binding [7].

We took advantage of the affinity of alkaline earth metal ions for saccharides and designed lipophilic alkaline earth metal complexes **1** in order to investigate the possibility of binding saccharides with these complexes in organic media. Here we report the liquid membrane transport [8] of monosaccharides using these lipophilic metal complexes **1** as carriers. Although a number of carriers including metal ion centers, so-called metallo-carriers, have been reported [9], substrates were limited to mostly ionic organic compounds like amino

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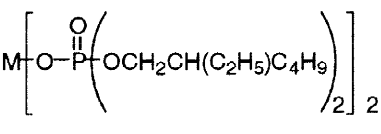
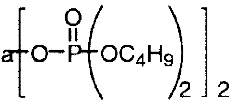
PII: S0040-4039(98)02229-1

acids. This is the first example of a metallo-carrier which is capable of transporting neutral monosaccharide molecules.



$M\left[O-\overset{O}{\overset{\|}{P}}\left(OCH_2CH(C_2H_5)C_4H_9\right)_2\right]_2$

1 M = Mg, Ca, Sr, Ba



$Ba\left[O-\overset{O}{\overset{\|}{P}}\left(OC_4H_9\right)_2\right]_2$

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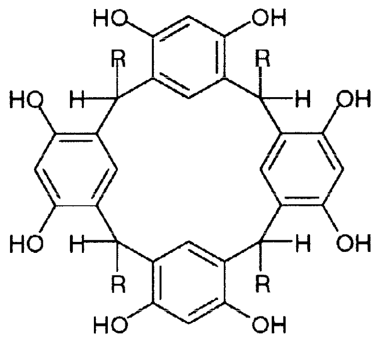
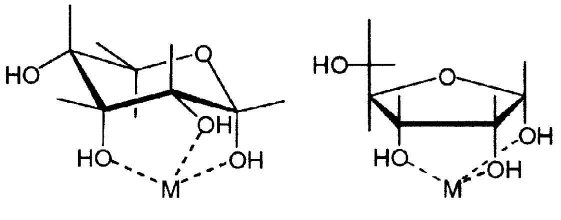


2 R = $(CH_2)_{10}CH_3$

Lipophilic alkaline earth metal complexes **1** were easily prepared by mixing the corresponding metal hydroxides with lipophilic phosphoric acid diesters in 1 : 2 molar ratio in chloroform at ambient temperature.[1] Several phosphoric acid diesters were tested and bis(2-ethylhexyl)hydrogen phosphate [10], which is commercially available as an extractant for rare earth metal ions, was found to be most suitable for attaining good solubility of the resulting complex. The transport experiments were done with a U-type glass cell across a chloroform liquid membrane from an aqueous source phase containing monosaccharide into a receiving phase (see foot notes of Table 1 for the details of transport conditions). The cell was kept at 25 °C and each phase was mechanically stirred at 200 rpm. At regular intervals, both aqueous phases were sampled, suitably diluted, and the concentration of monosaccharide was assayed by HPLC.[2]

Transport of ribose was investigated first because ribose is known to form stable complexes with alkaline earth metal salts in water owing to the suitable arrangement of three sequential hydroxyl groups for metal coordination, *i. e.*, an *axial-equatorial-axial* sequence in a *pyranose* form and a *cis-cis* sequence in a *furanose* form, as shown in Scheme 1 [11]. The initial transport rates and amounts of ribose transported after 48 h are summarized in Table 1. In control experiments conducted with no metal complex in the organic phase, it was confirmed that no monosaccharide, including ribose, was transported. It was also observed that phosphoric acid diester itself could not mediate the transport of any monosaccharides under the same conditions (see Run 6 in Table 1).



α - *pyranose* α - *furanose*

Scheme 1 Possible binding modes of D-ribose with metal ion [11]

All transport processes proceeded under almost neutral pH as shown in Table 1. Barium complex **1** (M = Ba) transported ribose most rapidly among metal complexes investigated. The transport rates of ribose decreased in the following order: barium> strontium> calcium> magnesium. A metal ion having a larger ionic radius and consequently a higher coordination number transports ribose more effectively. It should be noted that under same conditions, no transport of ribose was observed when resorcinol tetramer derivative **2**, which has been reported as a good extractant for ribose and several other monosaccharides [1a], was used as a carrier.

The results of the transport experiments of other monosaccharides by barium complex **1** (M

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[1] Complexes **1** were purified by precipitation from acetone solution and gave satisfactory spectroscopic and analytical data.

[2] Conditions of analyses: column, Asahipak NH2P-50; eluent, acetonitrile / water = 66 : 34; flow rate, 1 ml / min; temp., 25°C; RI detector.

= Ba) are summarized in Table 2. Fucose and fructose were transported moderately well with lower initial transport rates compared to ribose. On the other hand, neither galactose nor glucose could be transported. The same substrate dependence was also observed in the transport experiments using calcium complex **1** (M = Ca). These results indicate that the structure of monosaccharide as well as the kind of metal ion affects the transport efficiency significantly. As already mentioned, ribose binds with metal ions effectively due to the suitable arrangement of three sequential hydroxyl group. This fact was also confirmed by the result of 2-deoxyribose-transport, in which transport efficiency was lowered. In addition the

Table 1
Transport of ribose through liquid membranes [a]

Run	Carrier	Initial transport rate (mmol / h)	Amount of ribose transported after 48 h (mmol)	pH[b]	
				Source phase	Receiving phase
1	**1** (M = Mg)	< 0.01	0.2	6.86	6.88
2	**1** (M = Ca)	0.03	1.2	6.96	6.98
3	**1** (M = Sr)	0.08	2.5	6.79	6.83
4	**1** (M = Ba)	0.19	3.0	6.89	6.84
5	**2**	0	0	---	---
6	phosphate[c]	0	0	---	---

[a] Initial transport conditions: (source phase) 0.5 mol dm^{-3} of ribose, aqueous solution, 15 ml, (organic phase) 1 mmol of carrier in 30 ml chloroform, (receiving phase) 15 ml of water.
[b] Measured after 48 h. [c] 2 mmol of bis(2-ethylhexyl)phosphate was used.

Table 2
Transport of Monosaccharides by Barium Complex **1**[a]

Monosaccharide	Initial transport rate (mmol / h)	Amount of monosaccharide transported after 48 h (mmol)[b]
D-glucose	$\cong 0$	0.1 (0)
D-galactose	$\equiv 0$	0.1
D-mannose	0.01	0.4 (0.2)
D-ribose	0.19	3.0 (1.7)
D-2-deoxyribose	0.01	0.5
D-arabinose	< 0.01	0.4
D-xylose	< 0.01	0.3 (0.1)
D-fucose	0.02	0.7
L-rhamonose	0.01	0.4
D-fructose	0.01	0.7

[a] For initial transport conditions, see Table 1. [b] Figures in parentheses are the result of competitive transport experiment. Transport conditions were the same except that a solution (15 ml) containing four monosaccharides (0.3 mmol dm^{-3} each) was used as the source phase.

resulting ribose-metal-phosphate ternary complex may be lipophilic, because there is no exposure of uncoordinated hydroxyl group to the surrounding hydrophobic organic media, assuming that ribose exists in an α-pyranose form preferentially in an organic phase [1a]. Therefore the uptake of ribose into an organic phase proceeds smoothly. On the other hand, two hexoses, galactose and glucose, seem to have the most unfavorable structure for binding with lipophilic complexes. The better result of mannose-transport was probably due to its more suitable arrangement of hydroxyl groups.[3] Pentoses, other than ribose, were more lipophilic than hexoses as one can understand from the difference of the 5-substituent in its pyranose form, although their arrangement of hydroxyl groups were not as good as that of ribose. Hence transport was moderate. We also conducted the competitive transport of ribose, mannose, xylose, and glucose. The result of the transport is also shown in Table 2. High selectivities of ribose against other monosaccharides was achieved.

We have not been able to get sufficient information for clarifying the precise structure of ternary monosaccharide-metal-phosphate complexes in an organic phase yet. In the case of ribose, however, extraction experiments suggested the formation of a **1**• (ribose)$_2$ adduct.[4] Furthermore we succeeded in isolating the complex • (ribose)$_2$ adduct using barium complex **3**.[5] The formation of 1 : 2 adduct is plausible, if one considers that barium ion can take a high-coordination number (8-10 or more) [12], sufficient for accommodating two molecules of ribose.

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[3] For example, an axial-equatorial-axial structure of 1,2,3-hydroxy groups in β–pyranose form.

[4] Conditions of extraction experiments : aqueous phase (5 ml), 0.50 mol dm^{-3} monosaccharide; organic phase ($CHCl_3$, 5 ml) 0.10 mol dm^{-3} **1**. Shaken for 24 hr.

[5] **3** • (ribose)$_2$ adduct was recrystallized from methanol-acetone solution. mp 153-155°C. Anal: Calcd. for $BaC_{26}H_{56}O_{18}P_2$: C, 36.48; H , 6.59. Found: C, 36.63; H, 6.63%.