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Synthetic Noncyclic Ionophores with Multiple Carboxylate Groups for Alkaline Earth Metal Cations

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Abstract. A series of synthetic ionophores containing two carboxylic acid groups were synthesized as carriers for alkaline earth metal cations. Among them, the lipophilic derivative having a trimenthylene bridge and multiple quinaldate moieties selectively transported barium ion from the basic aqueous phase to the acidic aqueous phase through the bulk dichloromethane liquid membrane. The cation selectivity was explained by considering the fit of the cation diameter with the pseudocyclic cavity.

Key words: Synthetic ionophore, lipophilic quinaldic acid, alkaline earth metal transport, liquid membrane.

1. Introduction

Naturally occurring ionophores such as nigericin and lasalocid selectively transport alkali metal and alkaline earth metal cations across natural and artificial membranes [1]. A variety of model compounds have been synthesized in order to understand the transport properties of such ionophores [2, 3]. In regard to the transport of alkaline earth metal cations, dibasic acid derivatives are potentially useful as carriers [4, 5], though monobasic acid ionophores are also effective [6–8]. In addition, an appropriate design of the coordination site should be investigated for improving the cation selectivity. We recently found that synthetic ionophores having one quinaldic acid moeity possess a unique cation selectivity for alkali metal cations [9]. This discovery aroused our interest in examining the function of the quinaldate group as the recognition site of synthetic ionophores for alkaline earth metal cations. In this paper we describe the design of ionophores with multiple proton-ionizable groups containing one or two quinaldate moieties and their transport properties for alkaline earth metal cations.

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2. Experimental

^{1}H-NMR spectra at 400 MHz were obtained with a JEOL JNM-GSX-400 spectrometer using tetramethylsilane as an internal standard. IR spectra were obtained with a Hitachi 260-10 spectrometer. The mass spectra were measured with a JEOL JMS-DS 303 HF spectrometer at an ionization potential of 70 eV. 8-[2-(Octyloxy)ethoxy]quinaldic acid (**6**) and 8-(2-hydroxydecyloxy)quinaldic acid (**7**) were prepared according to the method described in the literature [9].

2.1. PREPARATION OF **1**

2-[8-(2-Carboxyquinolinyl)oxy]decanoic acid (**1**) was prepared by the following sequence. A mixture of methyl 8-hydroxyquinaldate (0.81 g, 4 mmol), K_2CO_3 (0.41 g, 3 mmol), and n-Bu_4NBr (TBAB, 0.39 g, 1.2 mmol, as a phase transfer catalyst) in CH_3CN (15 mL) was stirred at room temperature for 1 h. Methyl 2-bromodecanoate (1.59 g, 6 mmol) was then added at 50 °C and the mixture was refluxed for 45 h. After the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (100 mL). Insoluble matter was removed by filtration. The CH_2Cl_2 solution was washed with H_2O (50 mL) and then the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was dissolved in methanol (40 mL). The methanol solution was refluxed for 20 h in the presence of a few drops of H_2SO_4 and then neutralized with 15% $NaHCO_3$. After the methanol was evaporated, the residue was treated with short column chromatography on silica gel (acetone : hexane = 1 : 1 (vol/vol)) to yield 1.82 g of the crude product. Further silica gel chromatography (5% acetone in hexane) yielded 1.33 g (86%) of the pure methyl ester. The ester (0.6 g, 1.55 mmol) was saponified with a mixture of methanol (20 mL) and 0.6 M NaOH (7.7 mL) for 3 h at room temperature. After the methanol was evaporated, water (50 mL) was added to the residue and the mixture was extracted with ether (50 mL × 2) to remove the unreacted ester derivative. The aqueous layer was acidified with 5 M HCl to about pH 2 and then extracted with CH_2Cl_2 (50 mL × 2). The CH_2Cl_2 layer was concentrated to give 0.46 g (82%) of **1**. IR(neat) 3400–3000, 2900, 1700, 1600, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + D_2O) δ 0.83 (t, 3H), 1.22–1.39 (m, 10H), 1.54–1.63 (m, 2H), 2.00–2.08 (m, 2H), 5.03 (t, 1H), 7.14–7.16 (m, 1H), 7.58–7.65 (m, 2H), 8.12 (d, 1H), 8.49 (d, 1H); MS(FAB) m/z (relative intensity) 360 (M^+ + 1, 100). *Anal. Calcd.* for $C_{20}H_{25}O_5N$: C, 66.83; H, 7.01; N, 3.89. *Found*: C, 66.64; H, 6.94; N, 3.87.

2.2. PREPARATION OF **2**

1-[(2-Carboxyphenyl)oxy]-2-octyl-3-[8-(2-carboxyquinolinyl)oxy]propane (**2**) was prepared by the following sequence. To a stirred suspension of $LiAlH_4$ (7.59 g, 0.2 mol) in THF (200 mL) was added diethyl octylmalonate (**8**) (10.9 g, 40 mmol) over a period of 30 min and the mixture was refluxed for a further 4 h.

After cooling to room temperature, 5% NaOH (50 mL) was added to the mixture, and the mixture was washed with THF. After the filtrate was concentrated, water (60 mL) was added to the residue and extracted with CH_2Cl_2 (200 mL × 2). The CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated to give 7.02 g (93%) of crude 2-octyl-1,2-propanediol (**9**). To a stirred solution of **9** (7.0 g, 37.2 mmol) in benzene (50 mL) and fifteen drops of pyridine, thionyl chloride (18.3 g, 99.6 mmol) was added, keeping the temperature below 10 °C over a period of 1 h. The mixture was refluxed for another 4 h, neutralized with 15% K_2CO_3 and extracted with ether (100 mL × 2). The ether layer was dried over $MgSO_4$ and concentrated. Silica gel chromatography (hexane) gave 2-octyl-1,3-dichloropropane (**10**) (7.12 g, 85%). The reaction of **10** with methyl salicylate was carried out according to a procedure which was almost the same as that used for **1**, and methyl 2-[2-(chloromethyl)decyl]oxybenzoate (**11**) was purified by silica gel chromatography (10% CH_2Cl_2 in hexane) (41% yield). The reaction of **11** with methyl quinaldate was also performed according to a procedure which was almost the same as that used for **1**, and silica gel chromatography (5% methanol in chloroform) gave 8-[2-[2-methoxycarbonyl)phenyloxymethyl]decyloxy]quinaldic acid (**12**) in 38% yield.

A solution of **12** (0.27 g, 0.55 mmol) in ethanol (20 mL) with 1 M NaOH (1 mL) was refluxed for 4 h. After the solvent was evaporated, water (50 mL) was added to the residue and extracted with ether (20 mL) to remove the unreacted **12**. The aqueous layer was acidified with 1 M HCl to about pH 2 and extracted with CH_2Cl_2 (100 mL × 2). The CH_2Cl_2 layer was dried over $MgSO_4$ to give **2** (0.21 g, 80%). IR(neat) 3600–3000, 2920, 1700, 1600, 1250, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.86 (t, 3H), 1.26–1.40 (m, 10H), 1.48–1.54 (m, 2H), 1.70–1.76 (m, 2H), 2.62 (m, 1H), 4.31–4.40 (m, 2H), 4.50 (m, 2H), 7.10 (m, 2H), 7.20 (d, 1H, J = 7.8Hz), 7.51–7.56 (m, 2H), 760–764 (m, 1H), 8.10–8.13 (m, 1H), 8.27 (d, 1H, J = 8.3Hz), 8.38 (d, 1H, J = 8.3Hz), 8.5 (broad, 2H); MS(FAB) m/z (relative intensity) 480 (M^+ + 1, 100). *Anal. Calcd.* for $C_{28}H_{33}O_6N{\bullet}0.5H_2O$: C, 68.83; H, 7.01; N, 2.87. *Found*: C, 69.07; H, 7.20; N, 2.54.

2.3. PREPARATION OF 3

1-[(4-Carboxyphenyl)oxy]-2-octyl-3-[8-(2-carboxyquinolinyl)oxy]propane (**3**) was prepared by a synthetic procedure which was almost the same as that used for **2**: Yield 22% (based on the starting material, **10**); IR(neat) 3600–3000, 2920, 1700, 1600, 1250, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + D_2O) δ 0.82 (t, 3H), 1.19–1.24 (m, 10H), 1.40–1.50 (m, 2H), 1.58–1.64 (m, 2H), 2.38–2.42 (m, 1H), 4.25–4.35 (m, 4H), 7.08 (d, 2H, J = 8.8Hz), 7.34 (d, 1H, J = 7.3Hz), 7.57–7.65 (m, 2H), 7.87 (d, 2H, J = 8.8Hz), 8.10 (d, 1H, J = 8.8Hz), 8.47 (d, 1H, J = 8.3Hz); MS(FAB) m/z (relative intensity) 480 (M^+ + 1, 100). *Anal. Calcd.* for $C_{28}H_{33}O_6N$: C, 70.12; H, 6.94; N, 2.92. *Found*: C, 70.11; H, 6.97; N, 2.89.

2.4. PREPARATION OF **4**

1,5-Bis[8-(2-carboxyquinolinyl)oxy]-2-octyl-3-oxapentane (**4**) was prepared by the synthetic procedure, which was almost the same as that used for **2**. Yield 30% (based on the starting material, **10**); IR(neat) 3600–3000, 2920, 2850, 1710, 1600, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + D_2O) δ 0.85 (t, 3H), 1.20–1.38 (m, 10H), 1.52–1.58 (m, 2H), 1.78–1.84 (m, 2H), 2.75–2.80 (m, 1H), 4.48–4.56 (m, 4H), 7.28 (d, 2H, J = 7.8Hz), 7.38 (d, 2H, J = 8.3Hz), 7.56 (dd, 2H, J = 7.8, 8.3HZ), 8.19 (d, 2H, J = 8.3Hz), 8.28 (d, 2H, J = 8.3Hz); MS(FAB) m/z (relative intensity) 531 (M^+ + 1, 100). *Anal. Calcd.* for $C_{31}H_{34}O_6N_2 \bullet H_2O$: C, 67.86; H, 6.61; N, 5.10. *Found*: C, 67.88; H, 6.30; N, 5.12.

2.5. PREPARATION OF **5**

1,3-Bis[8-(2-carboxyquinolinyl)oxy]-2-octylpropane (**5**) was prepared by the following sequence. 1-Bromo-5-chloro-2-octyl-3-oxapentane (**13**) was prepared according to the method described in the literature [10]. The synthetic procedure was almost the same as that used for **2**: Yield 36% (based on the starting material, **13**); IR(neat) 3600–3400, 2950, 2900, 1740, 1620, 1580, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.85 (t, 3H), 1.20–1.33 (m, 10H), 1.42–1.54 (m, 2H), 1.68–1.76 (m, 2H), 4.18–4.52 (m, 7H), 7.14–7.18 (m, 2H), 7.42–7.47 (m, 2H), 7.53–7.60 (m, 2H), 8.16–8.21 (m, 2H), 8.25–8.31 (m, 2H), 8.62 (broad, 2H); MS(FAB) m/z (relative intensity) 561 (M^+ + 1, 100). *Anal. Calcd.* for $C_{32}H_{36}O_6N_2 \bullet 0.5H_2O$: C, 67.47; H, 6.55; N, 4.92. *Found*: C, 67.43; H, 6.69; N, 4.88.

2.6. LIQUID MEMBRANE TRANSPORT

Transport experiments were carried out in a U-shaped cell at 25 °C [9, 11]. An organic solution (20 mL) containing the ionophore was placed in the bottom of the cell, and two portions of aqueous solutions (10 mL) were carefully added on top of the organic solution. Both surface areas were 2.0 cm^2. The organic phase was magnetically stirred at 500 rpm. The details of the transport conditions are summarized in the footnotes of Table I. The receiving phase was sampled from four different cells after 12, 24, 36, and 48 h and analyzed for cation concentration using a Nippon Jarrel-Ash AA-8500 atomic absorption spectrometer. The value reported in Table I is the mean of four runs and the deviations from the mean were less than 10%.

3. Results and Discussion

We prepared five, new dicarboxylic ionophores (**1–5**) as shown in Figure 1.

Competitive passive transport experiments were carried out in a U-shaped cell at 25 °C [9, 11]. The source phase and receiving phase were made basic and acidic by addition of tris(hydroxymethyl)aminomethane (pH 10.0) and HCl (pH 2.0),

TABLE I. Competitive passive transport of alkaline earth metal cations by synthetic ionophores

Ionophore	Transport velocity (μ mol/h)				Selectivity
	Mg^{2+}	Ca^{2+}	Ba^{2+}	ΣM^{2+}	Ba^{2+}/Ca^{2+}
1	~0	0.03	0.08	0.11	2.7
2	~0	0.70	0.37	1.07	0.53
3	~0	0.06	0.13	0.20	2.2
4	~0	0.09	1.14	1.23	13
5	~0	0.35	0.94	1.29	2.7
6	~0	0.57	0.27	0.84	0.47
7	~0	0.26	0.60	0.86	2.3

Transport conditions: aqueous phase 1 (10 mL), $[MgCl_2] = [CaCl_2] = [BaCl_2] = 0.01$ M, $[NH_2C(CH_2OH)_3] = 0.05$ M (pH 10.0); organic phase (CH_2Cl_2, 20 mL), [Ionophore] = 2.5×10^{-4} M; aqueous phase 2 (10 mL), [HCl] = 0.01 M (pH 2.0).

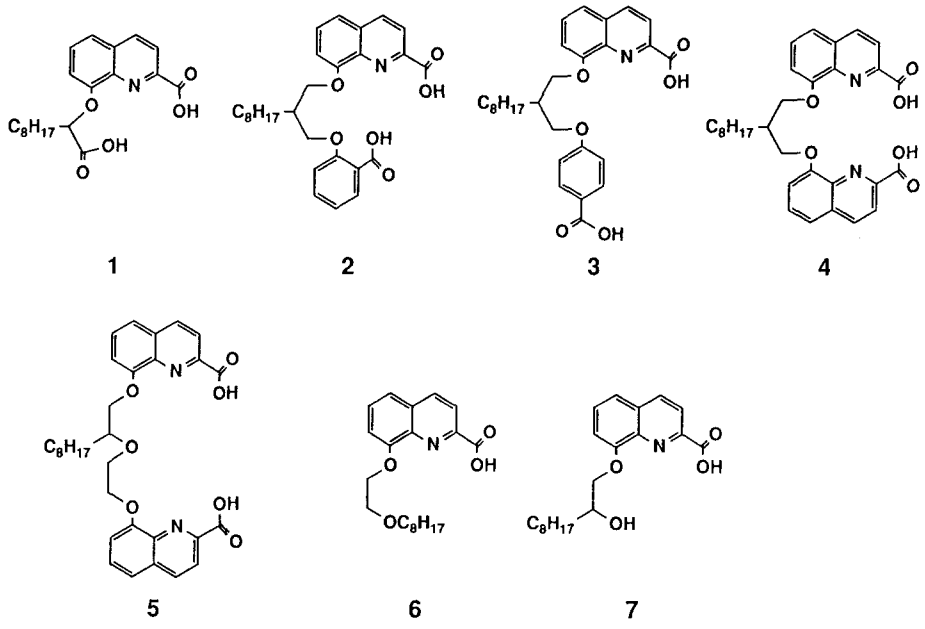

Fig. 1. Structures of the synthetic ionophores (**1–7**).

respectively. Alkaline earth metal cations were concentrated in the acidic phase by a coupled counter flow of protons. The amounts of transported cations are summarized in Table I. Mg^{2+} cations were scarcely transported by these synthetic ionophores possibly because of the high hydration energy.

Ionophores **4** and **5** selectively transported Ba^{2+} but ionophore **2** showed Ca^{2+} selectivity. The highest Ba^{2+} cation selectivity was observed for **4** among these ionophores. Since the size of the coordination space of the ionophore estimated by

CPK models examinations increases in the following order: **2** < **4** < **5**, this cation selectivity is reasonably explained by considering the fit of the cation diameter with the pseudo cyclic cavity. In the transport using ionophore **4**, the number of turnovers (cation transport cycles with the ionophore) was calculated to be about 5.5 per day, indicating that the cation transport by these ionophores was repeated.

The amounts of cations transported by ionophores **1** and **3** were relatively small. The size of the coordination space of **1** may be too small for Ca^{2+} and Ba^{2+}. Therefore, ionophore **1** is unable to effectively encapsulate the cation in the organic barrier. On the other hand, in the case of **3**, two carboxyl groups can hardly coordinate the same cation simultaneously due to the structural requirement, and thus may independently interact with different cations in the basic interface; it should be difficult for the ionophore to transfer the bivalent cation to the organic liquid membrane because of the insufficiency of the organophilicity.

The naturally occurring ionophore nigericin, which is one of the representative monocarboxylic antibiotics, selectively transported Ba^{2+} through a $CHCl_3$ bulk liquid membrane [4a]. Thus the transport using synthetic monocarboxylic ionophores **6** and **7** was also carried out. These ionophores (**6** and **7**) were selected as the carries for alkaline earth metal cations, because they showed a different cation selectivity in the transport of alkali metal cations, that is, **6** and **7** showed Li^+ and Na^+ selectivities, respectively [9]. The transport data obtained for alkali metal cations suggested that the ether oxygen of the octyloxy group of ionophore **6** hardly contributed to the cation recognition but the hydroxyl group of ionophore **7** participated in the binding. From this result, the coordination space of the latter of alkali metal cations is regarded to be larger than that of the former. In the transport of alkaline earth metal cations, ionophores **6** and **7** selectively transported Ca^{2+} and Ba^{2+}, respectively (Table I). Although these types of ionophores usually take up the bivalent cation as the 2 : 1 complex [1, 12], this result is consistent with the idea that the cation selectivity reflects the size of the coordination space; a good relationship between the cation size and the coordination size was also observed in these monobasic acid derivatives.

4. Conclusion

An appropriate arrangement of the coordination site considering the fit of sizes between the cation and the ionophore was shown to be of importance in the design of synthetic ionophores for alkaline earth metal cations.

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