Biomimetic Application of Natural Valinomycin and Nonactine Ionophores to Artificial Transport of Amino Acid Salts[1)]

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Synopsis. Biological valinomycin and nonactine ionophores showed new and interesting transport abilities for important amino acid salts in the biomimetic membrane systems, which are of biological interest and of practical significance.

Valinomycin and nonactine are typical biological ionophores,[2)] which strongly bind K^+ ion in their macrocyclic cavities and effectively transport it across a biomembrane. A variety of investigations of molecular structures, biological activities, and other chemical properties of these ionophores have been investigated, but most of them have focussed only on K^+ cation transport phenomena.[3)]

Here we present a new biomimetic application of biological valinomycin and nonactine ionophores to the artificial membrane transport, in which amino acid derivatives are transported as anionic or cationic guest species. Although valinomycin and nonactine ionophores are believed to act as K^+ ionophores, we found that they showed excellent transport abilities for several amino acid guest salts. Their transport properties are compared with those of synthetic biscrown **3** and cryptand **4** (Fig. 2), because they are known to form three dimensional complexes with K^+ cation.[4)] Typical transport results, obtained by using a $CHCl_3$ liquid membrane, are summarized in Table 1.

Valinomycin **1** and nonactine **2** effectively transported several amino acid derivative anions together with alkali metal cations in the same direction, as observed in some biological amino acid symport systems.[5)] Table 1 demonstrates that valinomycin showed higher transport efficiencies than nonactine and other synthetic ionophores. Its transport properties were significantly controlled by combination of guest anion and cotransported cation. Optimal combination of Cs^+ and *N*-benzoylphenylalanine anion(Bz–Phe^-) provided suitably stable "valinomycin-guest anion-cotransported cation" type complex and allowed high transport efficiency.[6)] Since other employed ionophores had favourable combinations of guest salts, an effective transport of a given amino acid salt could be realized by appropriate choice of the employed ionophore and cotransported cation. These results clearly reveal new and potential transport functionalities of well-known bio-ionophores.

Table 1 also indicates that valinomycin **1** and nonactine **2** hardly mediated transport of amino acid ester salts, though the NH_3^+-moiety of amino acid ester has an ionsize similar to that of K^+ cation. Since synthetic ionophores **3** and **4** mediated transport of amino acid ester salts, the rigid backbones and bulky residues of biological valinomycin and nonactine ionophores would prevent stable complexations with guest ammonium cations of bulky amino acid esters.

The present results provide new and significant insights of biological and practical membrane transport systems. Other types of biological ionophores may offer further interesting transport functionalities for a new series of guest species, though several struc-

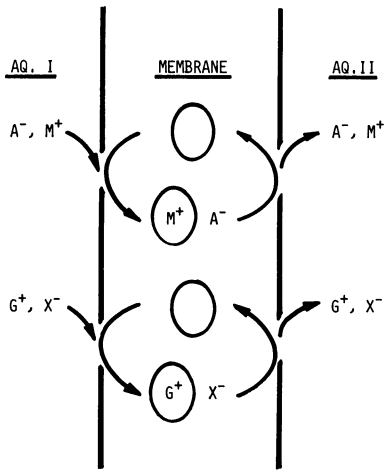

Fig. 1. Biomimetic membrane transport systems of amino acid salts.
O: Neutral ionophore; A^-M^+: *N*-Benzoylamino acid metal salt; G^+X^-: Amino acid ester salt.

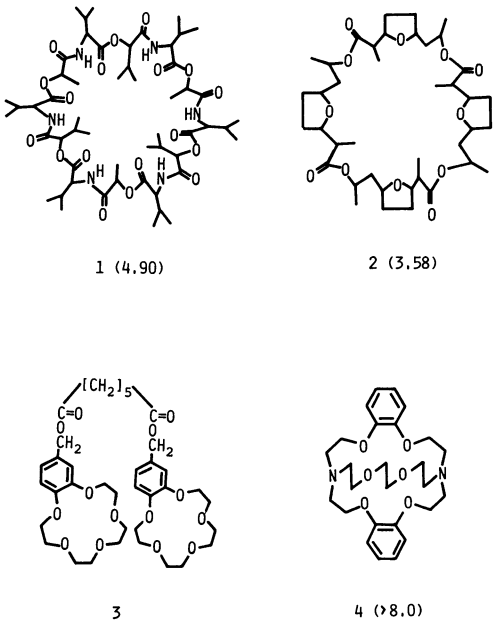

Fig. 2. Examined neutral ionophores.
The values indicated in parentheses were stability constants of the ionophores with K^+ ion in methanol as reported.

Table 1. Transport Properties of Amino Acid Salts by Neutral Ionophores

Guest Amino Acid Salt		Transport Rate $\times 10^6$ (mol/h)			
		1	2	3	4
A^-	M^+	"Condition A"			
Bz-Phe$^-$	Na^+	0.46	0.25	2.73	6.78
	K^+	8.80	4.88	2.68	1.57
	Cs^+	9.39	0.22	0.10	6.04
Bz-Leu$^-$	K^+	8.68	1.82	0.73	4.27
Bz-Val$^-$	K^+	7.56	0.72	0.24	4.29
Bz-Ala$^-$	K^+	4.57	0.16	0	2.11
G^+	X^-	"Condition B"			
H_3N^+-PheOEt	ClO_4^-	0	0.35	6.87	0.71
H_3N^+-TrpOMe	ClO_4^-	0	0	5.39	1.00

(Condition A) Aq. I: *N*-Benzoylamino acid, 0.5 mmol. MCl, 5.0 mmol. LiOH, 0.5 mmol/H_2O, 5 ml. Membrane: Ionophore, 0.0372 mmol/$CHCl_3$, 12 ml. Aq. II: H_2O, 5ml. (Condition B) Aq. I: Amino acid ester HCl, 0.5 mmol. $NaClO_4$, 1.0 mmol/H_2O, 5 ml. Membrane and Aq. II: same as Condition A.

tural modifications are required to suppress their high toxicities.

Experiments

1. Materials. Valinomycin, bis-crown, and cryptand ionophores were purchased from Aldrich, Dojindo, and Merck, respectively. Nonactine, obtained from Fluka, contained about 25% monactine. Special cares are required for usages of valinomycin and nonactine ionophores, because of their high toxicities. Other employed reagents were also commercially available and used without further purifications.

2. Transport Procedures. The transport experiments were carried out at room temperature in a U-tube glass cell (2.0 cm, i.d.) as reported before.[7] The ionophore in $CHCl_3$ (12 ml) was placed in the base of the U-tube, and two aqueous phases(5 ml, each) were placed in the arms of the U-tube, floating on the $CHCl_3$ membrane. The membrane phase was stirred with a magnetic stirrer. The amounts of amino acid derivative anions or cations transported into Aq. II phase were determined by spectroscopic method. Initial transport rates calculated are summarized in Table 1.

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