[Chem. Pharm. Bull. 36(8)3199—3201(1988)]

Selective Transport of Amines Mediated by Macrocycles Containing L-Amino Acids through a Liquid Membrane

HIROMI KATAOKA and TOYOSHI KATAGI*

Faculty of Pharmaceutical Science, Mukogawa University, 11–68 Koshien kyuban-cho, Nishinomiya, Hyogo 663, Japan

(Received March 28, 1988)

Affinity between several amines and macrocycles containing L-amino acid was found to result in efficient host-guest complexation. Transport of amines possessing an aromatic group or alkyl group was examined.

Keywords——Phe-containing macrocycle; Leu-containing macrocycle; carrier; selective transport; aromatic amine guest; aliphatic amine guest; host-guest complexation

Recently, we synthesized several novel macrocycles containing amino acid residues as constituents and examined their abilities for the selective transport of amino acid methyl esters through a liquid membrane.[1] It was found that some synthetic macrocycles exhibited quite different transport properties from those of 18-crown-6. For example, the synthetic macrocycles containing Phe or Leu residues preferentially transported hydrophobic amino acid methyl ester salts (Phe and Leu), while 18-crown-6 effectively transported hydrophilic amino acid methyl ester salts (Gly and Ser).

Also, as affinity between analogous substituents in hosts and guests promotes transport, PPL-30 was the most efficient carrier for the transport of Phe–OMe and LLL-30 gave the best results for Leu–OMe (Fig. 1). It seems very likely that the side chain residues of synthetic macrocycles play an important role in the selective transport of amino acid ester salts by recognizing analogous substituents. In order to confirm the above prediction for hosts and guests in complexation, we have measured the relative rates of transport of various amines, instead of amino acid ester salts, through a chloroform liquid membrane containing the macrocycles with amino acids as constituents (PPL-30 and LLL-30). Two types of amines were selected as guests; one type contained an aromatic ring [β-phenylethylamine salt (PEA) and benzylamine salt (BA)], and the other contained an alkyl side chain [isoamylamine salt (IAA) and isobutylamine salt (IBA)].

Experiments were conducted according to Kobuke *et al.*[2] The amounts of guest amines transported into the receiving phase were determined by gas liquid chromatography and the

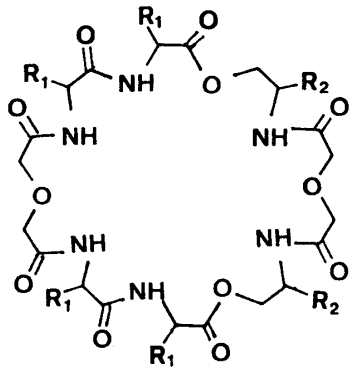

Fig. 1. Macrocycles Containing L-Amino Acids
$R_1 = CH_2C_6H_5$, $R_2 = CH_2CH(CH_3)_2$ (PPL-30)
$R_1 = R_2 = CH_2CH(CH_3)_2$ (LLL-30)

TABLE I. Amounts of Guest Amines (mM) Transported into the Receiving Phase[a]

Carrier	PEA	BA	IAA	IBA
PPL-30	15.64	2.43	2.22	0.48
LLL-30	6.17	2.71	6.56	0.68

a) Transport conditions: Aqueous source phase, 0.1 M guest and 0.2 M $LiPF_6$ in 2.5 ml of 0.08 M HCl; membrane, carrier (2.5 mM) in 10 ml of $CHCl_3$; aqueous receiving phase, 2.5 ml of 0.1 M HCl, 25 °C; 400 rpm.

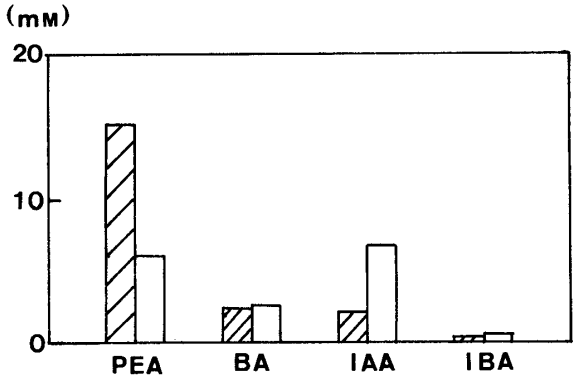

Fig. 2. Graphical Representation of the Transport of PEA, BA, IAA and IBA through a Liquid Membrane (mM)[a]

▨, PPL-30; □, LLL-30.

a) Transport conditions: Aqueous source phase, 0.1 M guest and 0.2 M $LiPF_6$ in 2.5 ml of 0.08 M HCl; membrane, carrier (2.5 mM) in 10 ml of $CHCl_3$; aqueous receiving phase, 2.5 ml of 0.1 M HCl; 25 °C, 400 rpm.

TABLE II. Association Constants (K_a) of Synthetic Macrocycles with Amines in Chloroform at 25 °C[a]

Host	K_a (M^{-1})	
	PEA	IAA
PPL-30	2700	190
LLL-30	380	380

a) Each value is the average of two or more independent determinations.

TABLE III. Partition Coefficients (P) of Guests between Chloroform and 0.08 M HCl at 25 °C[a]

Guest	P	Guest	P
PEA	8.1×10^{-2}	IAA	3.0×10^{-2}
BA	3.5×10^{-3}	IBA	1.5×10^{-4}

a) Each value is the average of two or more independent determinations.

results are shown in Table I and Fig. 2. The association constants (K_a) were also calculated by means of the equation reported previously[1] (Table II). In order to examine the hydrophobic nature of the four guest amines, their partition coefficients (P) between the source phase (0.08 M HCl) and the membrane solvent ($CHCl_3$) were also measured (Table III).

The synthetic Phe-containing macrocycle PPL-30 transported PEA, a hydrophobic guest containing an aromatic ring, more efficiently than BA and the others. The synthetic Leu-containing macrocycle LLL-30 transported IAA, a guest containing an alkyl side chain, in preference to the others. It seems noteworthy that each macrocycle has the ability to select an amine closely related to the constituent Phe or Leu as a suitable guest, such as PEA or IAA, but not BA or IBA. The LLL-30 transported PEA to some extent. In this case, the hydrophobic nature of PEA seems to play a role in host-guest complexation, besides the above structural recognition. The results imply that there is a subtle relationship between the efficiency of host-guest complexation and the lipophilicity of guests.

Experimental

A glass tube (1.6 cm i.d.) was placed in a cylindrical tube (2.6 cm i.d.) to separate two aqueous phases. The outer source phase containing 0.1 M guest and 0.2 M $LiPF_6$ in 2.5 ml of 0.08 M HCl and the inner receiving phase containing

2.5 ml of 0.1 M HCl were fixed. The organic phase consisting of 2.5 mM synthetic macrocycle in 10 ml of $CHCl_3$ was placed at the bottom of the cylindrical tube and stirred at 400 rpm by a magnetic stirrer at 25 °C. After 24 h, an aliquot of the receiving phase (0.5 ml) was withdrawn, and lyophilized. The residue was dissolved in ethyl acetate (0.5 ml), and then acetic anhydride (0.5 ml) and pyridine (0.1 ml) was added. The solution was permitted to stand at room temperature for 20 min. The amounts of guest amines transported into the receiving phase was determined by gas liquid chromatographic analyses using a Shimadzu GC-7AG (hydrogen flame ionization detector) equipped with a column (l = 1.6 m, i.d. = 3 mm) of 2% cyclohexanedimethanol succinate on Gas Chrom Q (80—100 mesh) which was developed with N_2 as a carrier gas at a flow rate of 50 ml/min. Quantitative analysis was performed by using *n*-paraffin as an internal standard (I.S.) (*n*-eicosane for acetyl-PEA, acetyl-BA and acetyl-IAA; *n*-octadecane for acetyl-IBA). The quantitative value was calculated by applying the following regression equations:

$$\text{acetyl-PEA};\ W = 1.09711A + 0.00745118$$

$$\text{acetyl-BA};\ W = 1.47268A - 0.0124204$$

$$\text{acetyl-IAA};\ W = 1.14527A + 0.025389$$

$$\text{acetyl-IBA};\ W = 1.93852A - 0.0186474$$

W = weight ratio (sample/I.S.)

A = area ratio (sample/I.S.)

Acknowledgement The authors are grateful to Professor Haruaki Yajima, Faculty of Pharmaceutical Science, Kyoto University, for valuable advice and discussions.

References

1) H. Kataoka and T. Katagi, *Tetrahedron*, **43**, 4519 (1987).
2) Y. Kobuke, K. Hanji, K. Horiguchi, M. Asada, Y. Nakayama and J. Furukawa, *J. Am. Chem. Soc.*, **98**, 7414 (1976).