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ACTIVE AND PASSIVE TRANSPORT OF AMINO ACID DERIVATIVES VIA METAL COMPLEX CARRIERS

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A new class of carrier, lipophilic copper complex, mediated active and passive transport of a variety of amino acid derivatives as carboxylate anion.

Carrier-mediated transport of amino acid derivatives plays essential roles in many biochemical processes.[1] It is very important to construct the model system of biological transport not only for simulating the biochemical systems, but also for developing a new methodology in the separation science. Although some kinds of polyethers[2] have been shown to transport ammonium cations derived from amino acids, we have known only a few synthetic carriers[3] for transporting amino acids as carboxylate anion, which may display largely different transport behaviors from those of previously reported cation-carriers.

Here we report that a new type of lipophilic copper complex carrier 1 successfully mediated active and passive transport of amino acid derivatives. In the present system (see Figure), metal complex, composed of neutral ligand (L), bound carboxylate anion (S^-) at interface of aqueous phase I and CH_2Cl_2 membrane. The coordinated carboxylate was carried through CH_2Cl_2 membrane, and released into the aqueous phase II. The antiport anion (X^-) was also transported in the opposite direction. The concentration gradient of antiport anion could drive active and passive transport of amino acid derivatives.

We examined four lipophilic copper complexes, 1, 2, 3, and 4, and trioctylmethyl-ammonium chloride 5 as anion carrier. The copper complex 1 was obtained

by mixing the neutral ligand $[CH_2CH_2N(CSNHPh)]_{n=8}$ and copper(II) chloride,[4] and soluble in CH_2Cl_2 membrane. The passive transport experiments were performed with a similar apparatus as described before.[5] The concentrations of amino acid derivatives in the aqueous phase II were determined by spectroscopic method, and initial rates obtained are listed in Table 1.

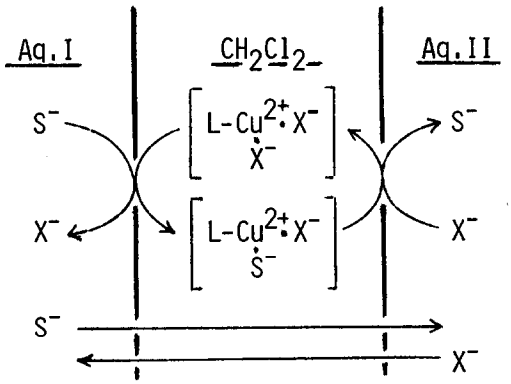

Fig. Used Liquid Membrane System.

Used Carrier:

1, $[CH_2CH_2N(CSNHPh)]_{n=8}$ - $CuCl_2$.[4]

2, tetrakis(trioctylamine)-copper(II) chloride.

3, bis(benzoylacetonato)copper(II).

4, bis(8-quinolinolato)copper(II).

5, trioctylmethyl-ammonium chloride.

Table 1. Carrier-Mediated Transport of Amino Acid Derivatives[a]

Substrate	Transport Rate[b] x 10^6 (mol/h)				
	1	2	3	4	5
Bz-Gly	21.3	13.6	0.2	0.4	21.6
Bz-Ala	18.5	16.1[e]	0.1	0.4	14.6
Bz-Glu	14.4[c]	13.8	0.3[e]	0.1	21.6
Bz-Gly-Gly	14.0[c]	10.9	0.3	0.1	20.4
Bz-Met	11.5	5.4[e]	0.1	0.1	14.4
Bz-Val	9.5	11.8[e]	0.1	0.1	10.0
Bz-Leu	9.5	4.6[e]	0.1	0.3	12.7
Bz-Phe	5.4	2.7[e]	0.1[e]	0.1	6.1
Ala	2.1[d]	-	-	-	5.2
Phe	1.2[d]	1.3[d]	2.2[d]	1.5	16.4

(a) Initial concentrations: Aq.I; substrate, 0.3 mmol / 0.1 N NaOH, 3ml. Aq.II; KCl, 5.0 mmol / H_2O, 9 ml. Membrane; carrier, 0.037 mmol / CH_2Cl_2, 8 ml. The organic phase was constantly stirred by a magnetic stirrer.

(b) Reproducibility; ± 15% or better. (c) Small amount of copper ion was moved into Aq.I.

(d) Leakage of copper ion was not negligible. (e) Copper species was partially suspended.

The carrier 1 transported a variety of N-benzoyl-amino acids with comparable efficiencies to those of a well-known anion carrier 5.[3] Under the employed conditions (see Table 1), the carrier 1 transported N-benzoylalanine in an amount equal to 57% of the total after 8 h and Cl^- (antiport anion) in the opposite direction.[6] We confirmed that the leakages of copper ion into the aqueous phases were usually small.[7]

The carrier 1 showed a quite interesting transport trend for the examined amino acid derivatives: Bz-Gly > Bz-Ala > Bz-Glu ~ Bz-Gly-Gly > Bz-Met > Bz-Val ~ Bz-Leu > Bz-Phe > Ala ~ Phe. This is largely different from that of previously reported transport system for non-substituted amino acids: Phe > Leu > Val > Ala > Gly.[3] Substitution by hydrophobic and bulky benzoyl group in the substrates clearly reflected on the transport behaviors.

Trioctylamine-$CuCl_2$ complex 2 (molar ratio of amine to $CuCl_2$: 4) also transported amino acid derivatives as carboxylate anion. When this complex was employed as carrier, large amounts of copper species were precipitated during the transport experiments, and its transport abilities were relatively lower than those of 1. In contrary to these complexes 1 and 2, anionic ligand coordinated copper complexes 3 and 4 hardly transported amino acid derivatives. These results suggest that formation of "substrate anion - copper ion - neutral ligand" ternary complex is essential in the present system.

Active transport of amino acid derivatives was attempted by using the present system where initial concentrations of substrate anion were same for both aqueous phases. The concentrations of substrate anion in both aqueous phases were followed, and apparently equilibrated concentrations (usually after 24 h) are listed in Table 2. When the antiport anion was added into the aqueous phase II, amino acid derivatives were successfully transported against their concentration gradients by aid of the carrier 1. The efficiency trend of active transport system was similar to that of passive transport system (see Table 1): Bz-Gly > Bz-Ala > Bz-Glu ~ Bz-Gly-Gly > Bz-Met > Bz-Val > Bz-Leu > Bz-Phe. This suggests that same factors govern both transport phenomena.

Table 2. Active Transport of Amino Acid Derivatives[a)]

Substrate	Carrier 1 in CH_2Cl_2 (mmol)	KCl in Aq.II (mmol)	Substrate Distribution (mmol)[b)]		
			Aq.I	CH_2Cl_2	Aq.II
Bz-Gly	0.056	0	0.219	0.062	0.219
	0.056	1.0	0.216	0	0.284
	0.056	2.5	0.122	0.005	0.373
	0.056	5.0	0.107	0.005	0.388
Bz-Ala	0.056	5.0	0.082	0.029	0.389
Bz-Glu	0.056	5.0	0.147	0.033	0.320
Bz-Gly-Gly	0.056	5.0	c)	c)	c)
Bz-Met	0.056	5.0	0.152	0.045	0.303
Bz-Val	0.056	5.0	0.157	0.073	0.270
Bz-Leu	0.056	5.0	0.159	0.082	0.259
Bz-Phe	0.056	5.0	0.143	0.105	0.252

a) These experiments were carried out in a U-shaped glass cell (i.d., 2.0 cm). Initial Concentrations: Aq.I; substrate, 0.250 mmol / 0.05 N NaOH, 5 ml. Aq.II; substrate, 0.250 mmol. KCl, 0 - 5.0 mmol / 0.05 N NaOH, 5 ml. Membrane; Carrier 1 / CH_2Cl_2, 12 ml. The organic phase was constantly stirred by a magnetic stirrer.

b) The concentrations of substrate in both aqueous phases were determined after 24 h.

c) Considerable amounts of copper ion were leaked into aqueous phases.

References and Notes

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4. The ligand $[CH_2CH_2N(CSNHPh)]_{n=8}$ (0.15 unit mmol) and $CuCl_2$ (0.037 mmol) were mixed in 20 ml of MeOH-CH_2Cl_2 solution (1:1, v/v) at ambient temperature for 30 min. After removal of solvent, the remaining green complex was used without further purifications. The copper ion may be coordinated by four thiocarbamoyl sulfur atoms in a square planar fashion. Ligand synthesis: H. Tsukube, T. Araki, H. Inoue, and A. Nakamura, J. Polym. Sci. Polym. Lett., 17, 437 (1979).
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6. We confirmed that antiport anion was also transported in the opposite direction by using ClO_4^- instead of Cl^-.
7. Under the employed conditions (see Table 1), ca. 7% of copper ion was leaked from membrane into aqueous phases after 12 h.

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