Artificial Transport of Amino-acid, Oligopeptide, and Related Anions by Macrocyclic Polyamine-Transition Metal Complex Carriers [1]

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Transition-metal complexes of the macrocyclic polyamine, 1,4,7,10-tetrabenzyl-1,4,7,10-tetra-azacyclododecane have been shown to be new and powerful ' metallo-carriers ' for the transport of amino-acid and oligopeptide derivatives. Their transport properties are generally different from previously reported systems, and are essentially controlled by factors such as the nature of the central metal ion, and the antiport anion. The metallo-carriers described provide both a successful example of artificial oligopeptide transport, and a unique and interesting transport phenomenon across a chloroform liquid membrane.

The membrane transport of organic substrates such as amino-acids, peptides, nucleic acids, and other biologically important species, has recently received much attention both in biology and chemistry. In particular, interest has focused on amino-acid and oligopeptide translocation in view of its importance in protein synthesis, cell growth, the metabolic cycle, and receptor/acceptor recognition. By using a variety of synthetic polyethers [2] and other types of carrier,[3] amino-acid derivatives have effectively and specifically been transported as the ammonium cation. In marked contrast, very few studies have been directed towards the development of a carrier capable of transporting amino-acid and oligopeptide derivatives as anionic species. Only scattered examples [4] of anion-host molecules have been presented: polyammonium and polyguanidinium salts act as anion complexones; quaternary ammonium salts allow artificial transport of amino-acids and phosphates.

Recently we demonstrated [5] that some transition-metal complexes employing linear multidentate and aromatic amine ligands could mediate both active and passive transport of amino-acid anions across a liquid membrane. These ' metallo-carriers ' provided characteristic functions in the transport process, and their transport efficiencies and selectivities could be regulated by factors such as the nature of the ligand molecule and co-ordinated metal ion.

Here we examine the macrocyclic polyamine, 1,4,7,10-tetrabenzyl-1,4,7,10-tetra-azacyclododecane (tbcyclen)–transition-metal complexes as the metallo-carrier candidate (see Figure 1). The following features are noteworthy. (i) The cyclic polyamine used, tbcyclen, is easily obtained in excellent yields (97%).[6] (ii) A number of transition-metal ions such as copper, nickel, and cobalt ions can be placed in the cavity of the cyclic polyamine ligand.[7] (iii) The co-ordination characters of the latter, *i.e.*, thermodynamic stability and strained geometry of 12-membered macrocyclic polyamine ligand, exert a considerable influence on the anion-co-ordination and transport process. (iv) The benzyl groups on the nitrogen atoms should create a hydrophobic micro-environment around the metal ion, displaying a good balance of hydrophobicity/hydrophilicity. (v) Steric crowding due to the benzyl groups may also allow the selective co-ordination of substrate anions. These structural features of tbcyclen and its complexes are markedly different from those of previously reported ' metallo-carriers ',[5] and should give rise to novel features in the transport process.

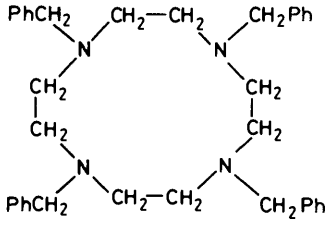
The present article describes the detailed results of the artificial transport of amino-acids, oligopeptides, and related anions by using new metallo-carriers; this offers a new possibility for the modelling of biomembrane transport systems. Experiments have been performed to elucidate the relationship between substrate structures (amino-acid sequence, chain-length, hydrophobicity, and terminal group) and transport efficiencies of macrocyclic polyamine-transition metal complexes. At the same time, effects arising from the nature of the central metal ion in the carrier and of the antiport anion employed are clearly demonstrated.

Metallo-carriers

[$CuCl_2$(tbcyclen)]
[$NiCl_2$(tbcyclen)]
[$CoCl_2$(tbcyclen)]

Surfactant-carriers

[$(Octyl)_3NMe$]Cl



(tbcyclen)

Figure 1. Anion transport carriers examined

Results and Discussion

Metallo-carrier and Liquid Membrane System.—Models of tbcyclen–metal complexes and the reported chemical/physical properties of the latter [7] suggest that tbcyclen is incapable of co-ordinating in a coplanar fashion with metal ions because of its cavity size; its metal complexes seem to be in a lower symmetry environment (approximately a square pyramidal or octahedral geometry). In these metal complexes, two co-ordinated anions appear to be non-equivalent, one being tightly co-ordinated to the metal ion, while the other is so-called ' labile ' and easily exchangeable. Such co-ordination properties of the tbcyclen-metal complexes are essentially different from those of previously reported metallo-carriers, and unique transport features are expected.

Two types of transport experiments were conducted. The active transport experiments of *N*-benzoylamino-acid anions were performed in an U-shaped cell similar to those previously described.[5] The metallo-carrier in chloroform was placed in the base of the U, and two aqueous solutions of equal amino-acid anion concentration and pH value were placed in the arms of the U, floating on the chloroform membrane. When the antiport anion salt, for example potassium chloride, was added into the aqueous phase II, amino-acid anion was transported from aqueous phase I to aqueous phase II against its concentration gradient, by means of the carrier. We confirmed that no diffusion was detected in the absence of carrier or in the absence of antiport anion. The transport process can be explained by a four-step reaction sequence (see Figure 2): (i) At the aqueous phase I/membrane interface, metallo-

Table 1. Active transport of *N*-benzoylamino-acid anions by metallo-carriers [a]

Metallo-carrier	Substrate	Antiport anion (mmol)	Equilibrated substrate distribution (mmol) [b] Aq. I	Membrane	Aq. II
$[CuCl_2(tbcyclen)]$	Bz-Gly	No	0.211	0.078	0.211
	Bz-Gly	Cl^- (2.5)	0.165	0.037	0.298
	Bz-Gly	Cl^- (5.0)	0.134	0.026	0.340
	Bz-Gly	Cl^- (10.0)	0.060	0.026	0.414
	Bz-Gly	ClO_4^- (5.0)	0.201	0.033	0.266
	Bz-Gly	SCN^- (5.0)	0.226	0.014	0.260
	Bz-Ala	Cl^- (5.0)	0.057	0.006	0.437
	Bz-Gly-Gly	Cl^- (5.0)	0.161	0.004	0.335
	Bz-Glu	Cl^- (5.0)	0.077	0	0.423
	Bz-Val	Cl^- (5.0)	0.105	0.040	0.355
	Bz-Met	Cl^- (5.0)	0.124	0.084	0.292
	Bz-Leu	Cl^- (5.0)	0.130	0.070	0.300
	Bz-Phe	Cl^- (5.0)	0.175	0.098	0.227
$[CoCl_2(tbcyclen)]$	Bz-Gly	Cl^- (5.0)	0.100	0.013	0.387
	Bz-Ala	Cl^- (5.0)	0.075	0.032	0.393
	Bz-Glu	Cl^- (5.0)	0.090	0.046	0.364
	Bz-Gly-Gly	Cl^- (5.0)	0.152	0.002	0.346
	Bz-Val	Cl^- (5.0)	0.132	0.078	0.290
	Bz-Met	Cl^- (5.0)	0.135	0.084	0.281
	Bz-Leu	Cl^- (5.0)	0.132	0.093	0.275
	Bz-Phe	Cl^- (5.0)	0.183	0.108	0.209
$[NiCl_2(tbcyclen)]$	Bz-Gly	Cl^- (5.0)	0.166	0.051	0.283
	Bz-Ala	Cl^- (5.0)	0.115	0.010	0.375
	Bz-Glu	Cl^- (5.0)	0.081	0.013	0.406
	Bz-Gly-Gly	Cl^- (5.0)	0.193	0.043	0.264
	Bz-Val	Cl^- (5.0)	0.143	0.053	0.304
	Bz-Met	Cl^- (5.0)	0.148	0.122	0.230
	Bz-Leu	Cl^- (5.0)	0.154	0.106	0.240
	Bz-Phe	Cl^- (5.0)	0.194	0.100	0.206
$(Octyl)_3NMe^+Cl^-$	Bz-Gly	Cl^- (5.0)	0.083	0.003	0.414
	Bz-Ala	Cl^- (5.0)	0.069	0.001	0.430
	Bz-Glu	Cl^- (5.0)	0.117	0.017	0.366
	Bz-Gly-Gly	Cl^- (5.0)	0.112	0.021	0.367
	Bz-Val	Cl^- (5.0)	0.117	0.021	0.362
	Bz-Met	Cl^- (5.0)	0.184	0.032	0.284
	Bz-Leu	Cl^- (5.0)	0.165	0.049	0.286
	Bz-Phe	Cl^- (5.0)	0.214	0.041	0.245

[a] Initial concentrations: aq. I; substrate, 0.250 mmol/0.05M-NaOH, 5 ml; aq. II; substrate, 0.250 mmol; antiport anion, 0—10 mmol/ 0.05M-NaOH, 5 ml; membrane; carrier, 0.056 mmol/ $CHCl_3$, 12 ml. [b] The concentrations of substrate anion in both aqueous phases were determined spectroscopically after 24 h. The indicated value is the average of three independent determinations, with an error of ±0.004 mmol.

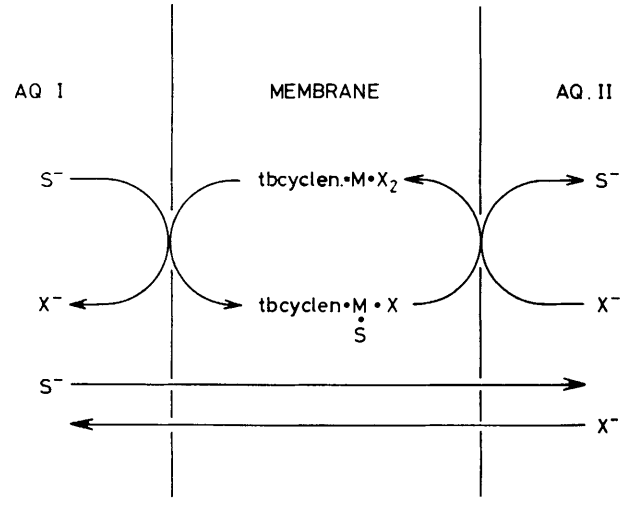


Figure 2. Liquid membrane containing 'metallo-carrier'; S^-: substrate anion; X^-: antiport anion; M: metal ion

carrier binds substrate anion (S^-) *via* co-ordinated anion exchange, and forms a 'substrate anion-metal ion-tbcyclen' ternary complex. (ii) The complex so formed diffuses across the membrane. (iii) At the membrane/aqueous phase II interface, release of substrate anion (S^-) and extraction of antiport anion (X^-) occur. (iv) The reconstituted metallo-carrier diffuses back to the aqueous phase I/membrane interface where the cycle starts again. Although a chemical reaction is not linked, this process can be called carrier-mediated active transport, and shows some similarities to biological amino-acid transport.[8] The concentrations of amino-acid anions in both aqueous phases were monitored spectroscopically, and the concentrations of each amino-acid anion apparently in an equilibrium state, usually after 24 h's operation, were determined. Passive transport experiments differed from above-mentioned experiments only in being the absence of substrate anion in the aqueous phase II (see Experimental section).[9] The transport rates shown were obtained from the rates of appearance of the substrate anion into the aqueous phase II.

Active Transport of N-*Benzoylamino-acid: Transport Properties of New Metallo-carriers.*—The new metallo-carrier, $[CuCl_2(tbcyclen)]$, for example, showed characteristic active transport selectivity for a series of *N*-benzoylamino-acid

anions (see Table 1): Bz-Ala > Bz-Glu > Bz-Gly ~ Bz-Gly-Gly ~ Bz-Val > Bz-Met ~ Bz-Leu > Bz-Phe. This order differs from those displayed by previously reported metallo-carriers,[5] $[CuCl_2\{CH_2CH_2N(CSNHPh)\}_8]$ and $[CuCl_2$(bathophenanthroline)], and conventional surfactant anion-carrier,[4a] trioctylmethylammonium chloride. Moreover, the actively transported amounts of the $[CuCl_2$(tbcyclen)] carrier system were found to be larger than those of the previously reported systems. These facts strongly suggest that the characteristics of the ligand used (*e.g.* co-ordination chemistry and lipophilic properties) are essential factors in determining transport behaviour in metallo-carrier systems.

The nature of the co-ordinated metal ion in the tbcyclen complex carrier was clearly reflected both in the transport efficiency and selectivity of the latter. Thus the copper- and cobalt-tbcyclen complexes had higher efficiencies in the active transport of amino-acid anions than the nickel-tbcyclen complex. The substrate specificity sequence displayed by metallo-carriers was also sensitively varied by a change in the central metal atom: thus the copper complex effectively transported Bz-Ala; the nickel-containing carrier favoured Bz-Glu; and the cobalt complex carried Bz-Gly with a higher rate. Since these metal complexes showed similar co-ordination geometry,[7] the co-ordination ability of the central metal ion may give rise to these different transport efficiencies.

Other transport experiments showed that chloride anion was a more effective antiport anion than perchlorate and thiocyanate anions, possibly being more easily exchanged by amino-acid anions at interfaces and thus giving rise to higher transport rates.* When the antiport anion was chloride, the concentration ratio of Bz-Gly anion across the membrane, $[Bz\text{-}Gly]_{aq,II}/[Bz\text{-}Gly]_{aq,I}$, rose after 24 h's operation from an initial value of 1, to 7. None of the previously reported metallo-carriers under comparable conditions showed such an increase.

In order to examine the origin of transport selectivity for a series of amino-acid anions, liquid-liquid extraction experiments for each elementary process were carried out using $[CuCl_2$(tbcyclen)]. The results are illustrated in Figure 3, in which the actively transported amounts of amino-acid anions are also included for comparison.

The $[CuCl_2$(tbcyclen)] complex showed a higher extraction capability for a series of amino-acid anions than previously reported metallo-carriers;† their extraction profiles were changed in the presence of chloride anion in the aqueous phase probably as a result of competitive co-ordination between chloride anion and amino-acid anion. As a result, extraction percentages of amino-acid anions, especially hydrophilic substrates such as Bz-Gly, Bz-Ala, Bz-Gly-Gly, and Bz-Glu, were significantly lowered, but extraction selectivities for some hydrophobic amino-acid anions such as Bz-Phe, Bz-Leu, and Bz-Val, were relatively enhanced. These extraction trends parallel those described previously. The substrate anion-releasing process is therefore important in the present transport system.

A surfactant carrier displayed a similar pattern of extraction behaviour, but with a higher extraction capability for some hydrophilic amino-acid derivatives. Although its transport selectivity seemed to be almost parallel to that of extraction

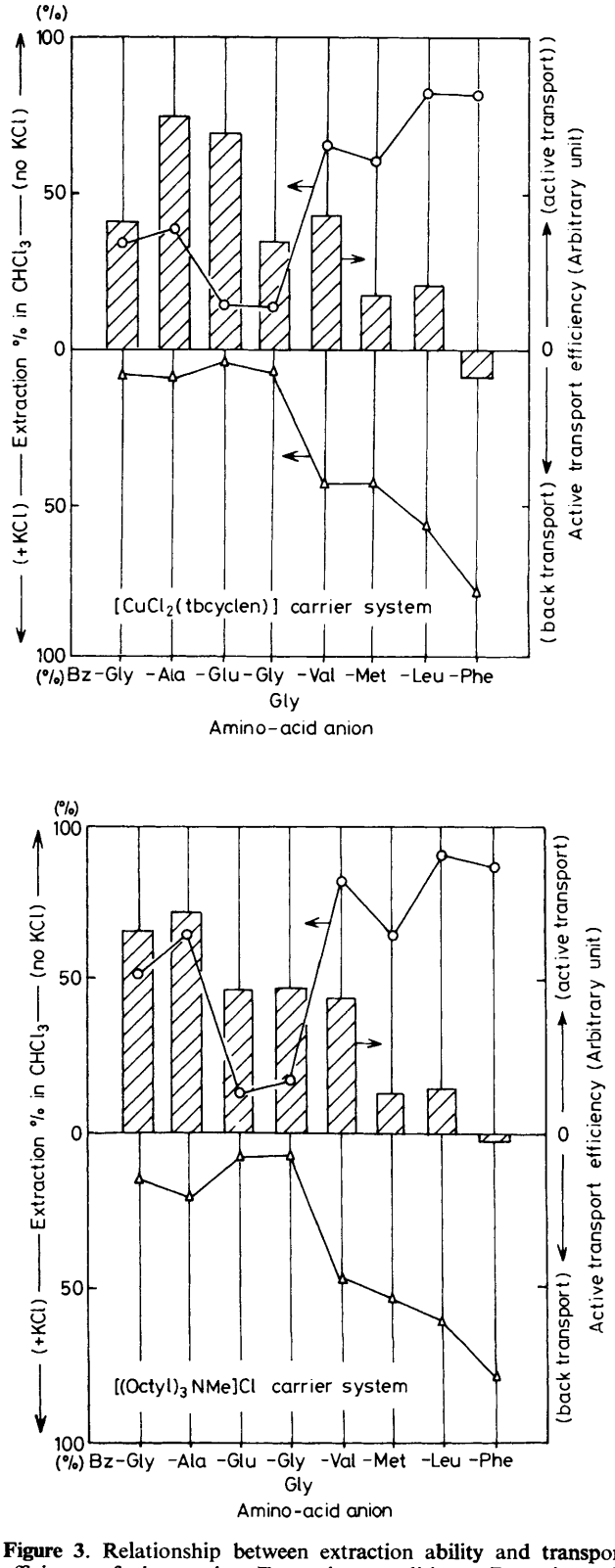


Figure 3. Relationship between extraction ability and transport efficiency of the carrier. Extraction conditions: Bz-amino-acid (0.0186 mmol), KCl (0 or 0.8 mmol) in 0.05M-NaOH (4 ml)/carrier (0.0280 mmol) in $CHCl_3$ (4 ml)

* A similar antiport anion effect has already been observed in an artificial ADP-transport system; see ref. 4c.

† Previously reported metallo-carriers have showed lower extraction capabilities under the comparable conditions (in the absence of KCl) $[CuCl_2\{CH_2CH_2N(CSNHPh)\}_8]$; Bz-Phe, 60.3%; Bz-Leu, 31.8%; Bz-Val, 28.9%; $[CuCl_2$(bathophenanthroline)]; Bz-Phe, 48.7%; Bz-Leu, 27.3%; Bz-Val, 17.6%.

Table 2. Artificial transport of oligopeptide derivatives by metallo-carriers [a]

Substrate	Transport rate × 10^6 (mol/h)			
	[(Octyl)$_3$NMe]Cl	[$CuCl_2$(tbcyclen)]	[$NiCl_2$(tbcyclen)]	[$CoCl_2$(tbcyclen)]
Z-Gly	18.5	10.7	13.4	9.8
Z-Ala	19.1	10.6	9.5	7.0
Z-Leu	6.7	5.3	3.9	5.4
Z-Phe	3.1	2.8	1.6	2.4
Z-Gly-Gly	19.5	14.1	14.3	18.1
Z-Gly-Ala	20.8	16.6	13.4	20.9
Z-Gly-Leu	12.5	12.8	7.1	10.5
Z-Gly-Phe	6.8	9.7	5.5	7.2
Z-Gly-Gly-Gly	6.9	6.5	4.1	8.5
Z-Gly-Gly-Ala	10.2	9.1	10.5	13.3
Z-Gly-Gly-Leu	11.4	12.3	8.4	9.0
Z-Gly-Gly-Phe	13.1	7.8	11.1	12.3

[a] Initial concentrations: aq. I; substrate, 0.15 mmol/0.05M-NaOH, 3 ml; aq. II; KCl, 9.0 mmol/distilled water, 9 ml; membrane; carrier, 0.0372 mmol/$CHCl_3$, 8 ml. Initial rates were shown in the Table. Each value is the average of two or more independent determinations. The experimental values deviate from the reported values by an average of ±15% or better.

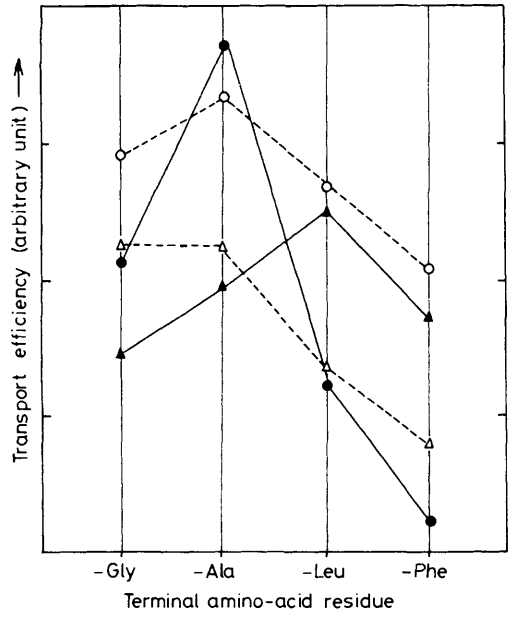


Figure 4. Graphical representation of transport efficiency of [$CuCl_2$(tbcyclen)] carrier for various peptide substrates: ● = Bz-, △ = Z-; ○ = Z-Gly-; ▲ = Z-Gly-Gly-

experiments in the presence of chloride anion, other factors should be considered in the case of Bz-Gly and Bz-Ala transport systems, notably the facile extraction tendency of these substrates. The transport selectivity of the surfactant-mediated system would be governed by a combination of the extraction rates into and releasing rates from the membrane.

Recently some macrocyclic polyethers were found to mediate successfully active transport of amino-acid anions, coupled with potassium cation transport.[10] In this system, amino-acid anions with higher hydrophobicities allowed effective transport, and their transport efficiency sequence was as follows: Bz-Phe > Bz-Leu ~ Bz-Met > Bz-Val > Bz-His ~ Bz-Ala ~ Bz-Gly-Gly ~ Bz-Gly. Such a transport trend indicates that a substrate anion-extraction process into the membrane by complexation with a potassium-polyether cation complex is important in contrast to the present metallo-carrier system, thus, transport selectivity for a series of amino-acid anions could be effectively controlled by appropriate choice of the carrier employed.

Artificial Peptide Transport by Metallo-carrier.—New metallo-carriers were applied to the transport of amino-acid, dipeptide, and tripeptide derivatives. The previously reported metallo-carrier, [$CuCl_2${CH_2CH_2N(CSNHPh)}$_8$] appeared of little use for peptide transport, since competitive co-ordination of the ligand molecule and substrate anion to the copper ion resulted in decomposition of the original metallo-carrier complex.[5] On the other hand, the present macrocyclic polyamine-transition metal complexes have thermodynamic stabilities high enough for them to act as peptide transport carriers.

The tbcyclen-metal complexes employed were found to mediate artificial transport of amino-acid, dipeptide, and tripeptide derivatives with rates comparable to those of a conventional surfactant carrier. Typical results are listed in Table 2, and illustrated in Figure 4. It was important that they displayed different patterns of transport behaviour to those of a surfactant carrier. Although similar ion-pairing interactions between carrier and substrate anion are expected to play a major role in both carrier systems, [$NiCl_2$(tbcyclen)], in particular, showed unique transport selectivity for a series of Z-amino acids and Z-tripeptides. Therefore, in principle, metal co-ordination interaction should give rise to novel transport phenomena.

Substrate specificity for a series of Z-amino-acid anions was generally parallel to that observed in the active transport of Bz-amino acid anions: Z-Gly ≳ Z-Ala > Z-Leu > Z-Phe. It has already been established in preceding papers [5] that Bz-Phe, Bz-Leu, and other hydrophobic amino-acid derivatives are effectively accumulated in the membrane, hardly being released into the aqueous phase II. A similar trend was observed in the transport of dipeptide analogues: Z-Gly-*Gly* ≳ Z-Gly-*Ala* > Z-Gly-*Leu* > Z-Gly-*Phe*. It was notable, however, that dipeptide anions were transported with higher rates than those of the corresponding amino-acid anions: Z-Gly-*Gly* > Z-*Gly*; Z-Gly-*Ala* > Z-*Ala*; Z-Gly-*Leu* > Z-*Leu*; Z-Gly-*Phe* > Z-*Phe*. An increase in the amino-acid sequence should lead to enhancement of the hydrophobicities of the substrate anions and of steric crowding around the co-ordination sites: the former would be expected to promote the rates of extraction into the membrane, and the latter to accelerate the rates of release into the aqueous phase II.

Such chain-length effects were emphasized in the tripeptide transport system, and contributed to create a unique substrate selectivity sequence: Z-Gly-Gly-*Gly* < Z-Gly-Gly-*Ala* ≲ Z-Gly-Gly-*Leu* ≲ Z-Gly-Gly-*Phe*. This is apparently contrary to that of the Z-amino-acid anion series mentioned above, and

is ascribed to a pronounced decrease in the transport rates of Gly- and Ala-containing tripeptides.

These results suggest that a carrier-mediated peptide transport process could be controlled by a combination of factors including the hydrophobicities of substrate anions and steric factors around the co-ordination sites. In Z-amino-acid and Z-dipeptide transport systems, hydrophobic substrates would be accumulated in the membrane, but not effectively transported. On the other hand, Z-tripeptides have hydrophobicities high enough for them to be extracted into the membrane *via* complexation, the bulky residues of -Phe and -Leu of the tripeptides preventing stable complex formation and resulting in promotion of the release process.

The nature of the co-ordinated metal ions greatly influenced the transport behaviours (see Table 2). While the nickel complex more effectively mediated transport of Gly- and Ala-containing substrates, the copper complex seemed to provide relatively fast transport of Leu- and Phe-containing substrates. The cobalt complex carrier allowed higher transport rates for some dipeptides. Although the origin of these metal-ion effects is unclear, it is expected that transition-metal ions in the hydrophobic microenvironment fostered by the tbcyclen ligand would favourably control the co-ordination of peptide anions, as found in many metallo-enzymes.

The present transport system may provide an artificial analogue to the biological active transport of amino-acid and peptide derivatives,* and be considered as a prototype for the design of specific anion transport membranes. A number of variations and extensions can be envisaged either for use as biological models or for potential application.

Experimental

Materials.—The inorganic salts were reagent grade and employed as received. The *N*-benzyloxycarbonylamino-acids and -oligopeptides used were purchased from Sigma Chem. Comp. The *N*-benzoyl-glycine, -alanine, -valine, and -phenylalanine were purchased from Nakarai Chem. Ltd., and other benzoyl-amino acids were obtained from Tokyo Chem. Ind. Co. Ltd.

Carrier Synthesis.—The ligand tbcyclen and its metal complexes were prepared according to literature methods. To stirred aqueous sodium hydroxide (18 g/10 ml) at 5 °C or below, aziridine (19.5 g) was added; benzyl chloride (37.8 g) was then added dropwise. Stirring of the mixture was continued at room temperature for 3 h. The product, 1-benzylaziridine, was extracted with ether, and distilled under the reduced pressure (80—82 °C/10 mmHg);[11] yield 80%; δ ($CDCl_3$) 1.21 (m, 2 H, azir. H), 1.80 (m, 2 H, azir. H), 3.16 (s, 2 H, benzyl H), and 7.30 (m, 5 H, ArH).

Tbcyclen was prepared in nearly quantitative yield by refluxing a mixture of 1-benzylaziridine (10 g) and toluene-*p*-sulphonic acid (0.05 g) in 95% alcohol (75 ml) for 6 h.[6] The precipitated white solid, recrystallized from methanol–dichloromethane, had m.p. 142—143 °C; δ ($CDCl_3$) 2.66 (s, 16 H, ring H), 3.40 (s, 8 H, benzyl H), and 7.15 (m, 20 H, ArH).

Tbcyclen-$CuCl_2$, -$CoCl_2$, and -$NiCl_2$ complexes were prepared by refluxing a mixture of tbcyclen and the metal chloride (0.0558 mmol, each) in methanol–dichloromethane (30 ml; 1 : 1, v/v) for 3 h. After removal of solvent, the resulting material was employed without further purification. Their spectral profiles were identified with those reported.[7]

Transport Experiments.—The active transport experiment of *N*-benzoylamino-acids (Table 1) was performed in an U-shaped glass cell (2.0 cm, i.d.) as described before.[5] The concentrations of substrate anion in the aqueous phase II were increased with operation time, and reached at steady state (usually after 20—24 h). The concentrations of substrate anion in the aqueous phase I also decreased at similar rates. The apparently equilibrated concentrations are listed in Table 1.

The passive transport experiments (Table 2) were carried out in an apparatus similar to that described before.[9] A cylindrical glass cell (4.0 cm, i.d.) holding a glass tube (2.0 cm, i.d.) separated the two aqueous phases. The inner aqueous phase I contained substrate in alkaline solution (3 ml). The outer aqueous phase II contained distilled water (9 ml). The chloroform phase (8 ml) lying below these two aqueous phases, bridged them. The chloroform layer was stirred constantly by magnetic stirrer. The transport rate was calculated from the initial rate of appearance (determined spectroscopically) of substrate anion in the aqueous phase II. Reproducibility was confirmed as ±15% or better.

A similar transport experiment was carried out in the absence of carrier for reference. The detailed conditions are included in Table 2.

Liquid–Liquid Extraction Experiment.—The chloroform solution of carrier was in contact with an aqueous solution of the sodium salt of the substrate anion. After a given period, an organic phase was separated from the aqueous phase. The amount of extracted substrate anion was calculated from the difference between the initial and remaining substrate anion concentrations in the aqueous phase. The detailed conditions are shown in Figure 3.

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