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Macrocyclic pseudopeptides containing *N,N'*-ethylene-bridged-dipeptide units: synthesis, binding properties toward metal and organic ammonium cations, and conformations. The first step in designing artificial metalloproteins

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Contents

Abstract

To design a metalloprotein and metalloenzyme model, macrocyclic pseudopeptides containing *N,N'*-ethylene-bridged-dipeptides were synthesized and their conformations estimated. Piperazin-2-one rings in this type of macrocyclic pseudopeptide provide a hydrophobic wall and deep cavity as shown in the structure of valinomycin. A 24-membered cyclic pseudopeptide was able to include metal cations, and a 36-membered one was able to bind organic ammonium cations enantioselectively. This offers a new type of host–guest chemistry.

Keywords: Host–guest chemistry; Macrocyclic pseudopeptides; Macrocyclic peptides

1. Introduction

In the active sites of most metalloproteins and metalloenzymes, only functional groups such as imidazole, thiol and carboxylate on the side chains of amino acids

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bind to metal cations and fix the structure. As simple structural model compounds to these active sites of metalloproteins, Kojima synthesized the metal complexes with amino acid anhydrides (Fig. 1) [1–3]. This is a good model for such proteins, but he was limited in designing a protein model using amino acid anhydrides, since these complexes have no part which includes the substrates.

There are metal centers and hydrophobic pockets in metalloproteins (Fig. 2). Thus, the authors believed that two requirements must be met in designing the model:

(1) use of functional groups on the side chains of amino acids

(2) formation of a hydrophobic pocket (as shown in cyclodextrine)

Macrocyclic peptides have the potential to create novel compounds which meet these two conditions [4–6]. Laussac et al. synthesized cyclo(Gly-L-His-Gly-L-His-Gly-L-His-Gly) and revealed an interesting feature: three imidazole groups interacted

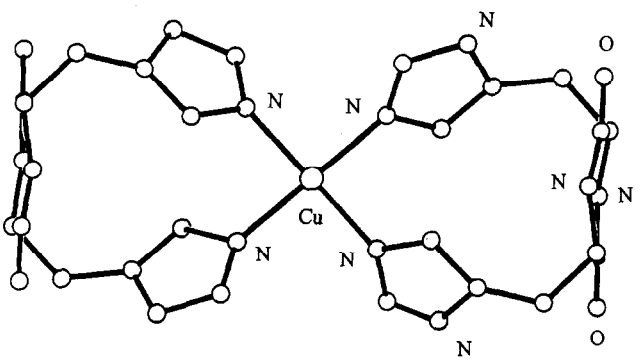


Fig. 1. Structure of $Cu[cyclo(L\text{-}His\text{-}L\text{-}His)]_2^{2+}$ (reproduced with permission from Ref. [2]).

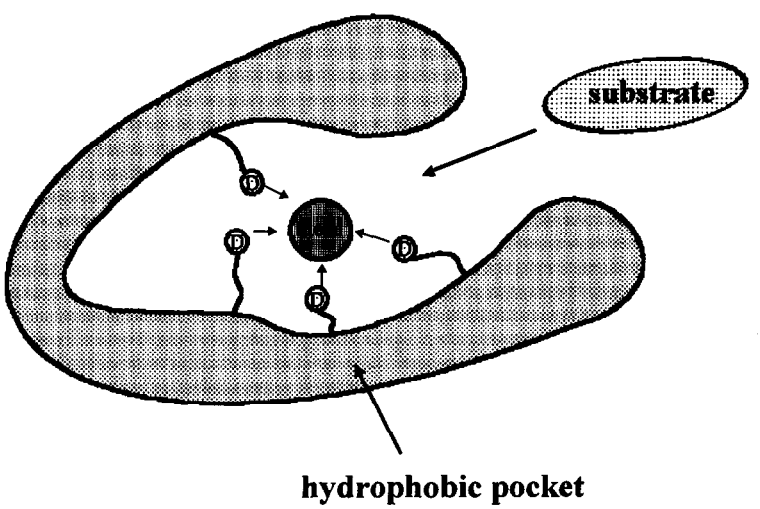


Fig. 2. Schematic representation of metalloprotein including substrate.

with Cu(II) at neutral pH (Fig. 3(a)) and four Gly NH deprotonated peptide nitrogens bound to Cu(II) at basic pH (Fig. 3(b)) [7]. However, macrocyclic peptides containing only natural amino acid residues generally have several disadvantages. Synthesis is often difficult owing to low solubility; control of conformation is also difficult; their cavities are not deep, as observed in cyclodextrine and cyclophane systems; intramolecular hydrogen bonds block their cavities and prevent the inclusion of substrates. Therefore, the authors designed and synthesized *N,N'*-ethylene-bridged dipeptides, eXX (Fig. 4), and used them as units of macrocyclic peptides [8,9]. This type of pseudopeptide has been thought to have no significant intramolecular hydrogen bonds (Fig. 5) [10,11] and to be highly soluble in organic media. The macrocyclic pseudopeptide with functional side chains would meet the above two conditions (Fig. 6), i.e. complexation with metal cations and inclusion of organic substrates. However, no macrocyclic pseudopeptide containing amino acid with functional groups on its side chain had yet been synthesized, so the first step was to obtain information on the conformation and characterization for molecular design. For this, the authors focused on the neutral ionophorous properties and chiral recognition properties of these peptides. In this account, the authors review the synthesis and the structures of the macrocyclic pseudopeptides containing

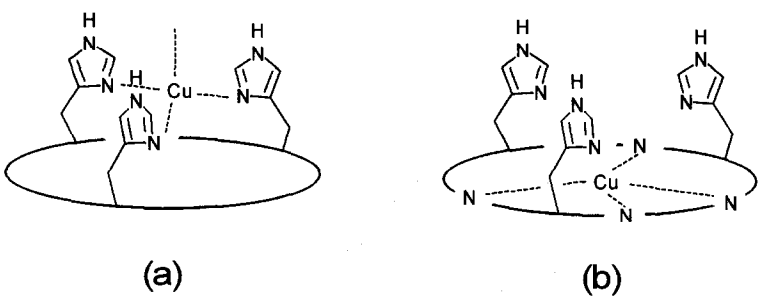
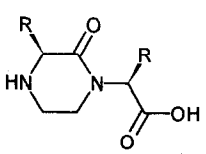


Fig. 3. Schematic representation of the Cu(II)–cyclo(Gly-L-His-Gly-L-His-Gly-L-His-Gly) complex: (a) at neutral pH and (b) at basic pH (adapted from Ref. [7]).



H-eXX-OH

X = L : R = $CH_2CH(CH_3)_2$
V : $CH(CH_3)_2$
A : CH_3
F : $CH_2C_6H_5$

Fig. 4. *N,N'*-ethylene-bridged dipeptides.

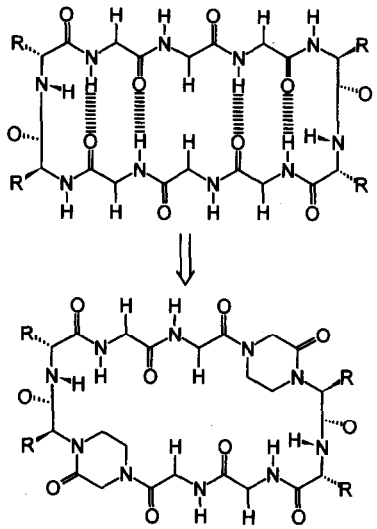


Fig. 5. Disappearance of intramolecular hydrogen bonds in macrocyclic pseudopeptide by *N,N'* ethylene bridges.

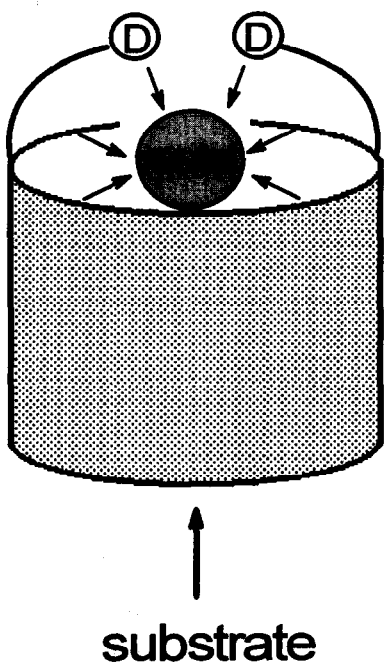
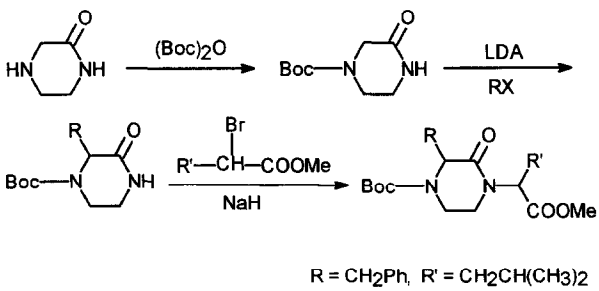


Fig. 6. Schematic representation of metalloprotein model using cyclic pseudopeptide.

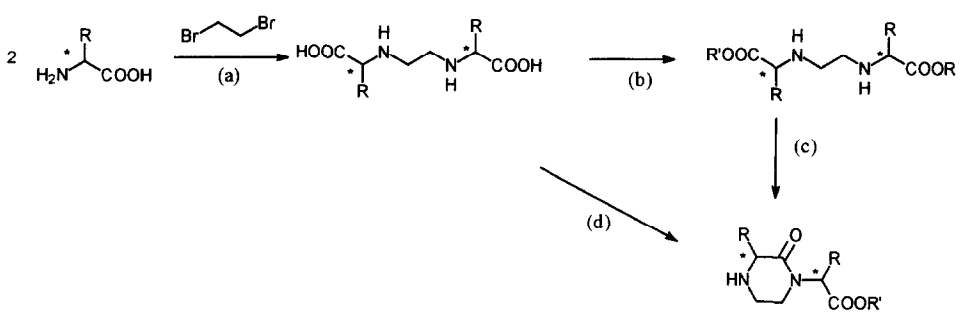
N,N'-ethylene-bridged dipeptide units and the complexations with metal cations and ammonium cations known to date.

2. Synthesis of *N,N'*-ethylene-bridged dipeptide units

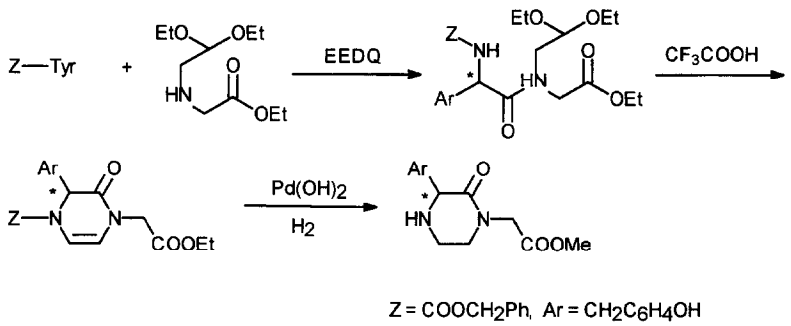
Moon et al. prepared *N,N'*-ethylene-bridged-phenylalanyl-leucine in 1981 to use as enkepharine analogues, but their method gave the mixtures of enantiomer and diastereomer (Scheme 1) [12]. A chiral dipeptide (*N,N'*-ethylene-bridged (*S*)-alanyl-(*S*)-alanine) was synthesized by Kojima et al. and first used as the unit of macrocyclic peptides in 1987 [8]. The dipeptide was obtained in boiling xylene by dehydrating the diester of *N,N'*-ethylene-bridged-bis-(*S*)-alanine obtained by a method similar to that of Scoenberg et al. (route (a)→(b)→(c) in Scheme 2) [13]. DiMaio and Belleau prepared *N,N'*-ethylene-bridged (*S*)-tyrosyl-glycine in 1989 (Scheme 3) [14], using catalytic reduction. This is not suitable for preparing *N,N'*-ethylene-bridged dipeptide containing sulfur atom as methionine. In 1993 Yamashita et al. synthesized *N,N'*-ethylene-bridged (*S*)-methionyl-(*S*)-methionine in two steps with acid-catalyzed cyclization of *N,N'*-ethylene-bridged bis-α-amino acid (route (a)→(b)→(d) in Scheme 2) and applied this to the preparation of enkepharine analogues [15].



Scheme 1. Synthesis of *N,N'*-ethylene-bridged phenylalanyl-leucine (eFG) by Moon et al.



Scheme 2. Synthesis of *N,N'*-ethylene-bridged dipeptide: (a) NaOH aq, K_2CO_3 aq; (b) $SOCl_2$, R'OH; (c) reflux in xylene for several days; (d) H^+, R'OH.

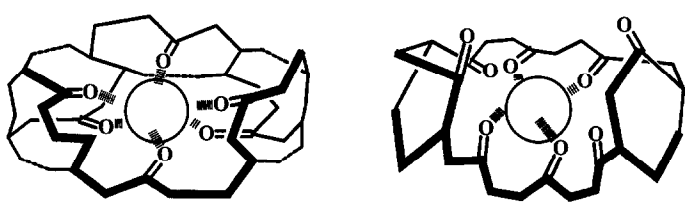


Scheme 3. Synthesis of *N,N'*-ethylene-bridged (*S*)-tyrosyl-glycine (eYG) by DiMaio et al.

3. Macrocyclic peptide as ionophore

Nature has many types of compound which vastly increase the permeability of membranes to particular ions; these are called 'ionophores'. These ionophores contain such polar ligating groups as carbonyl, lactone, catecholate and hydroxamate to bind metal cations. The classification and binding properties of several natural ionophores were previously described in detail by Tsukube [16], and Cox and Schneider [17]. Artificial macrocycles which mimic the essence of these ionophores have very interesting potential for novel functions.

The naturally occurring ionophore 'valinomycin' which selectively transports K^+ through the biomembrane has been studied by many. In valinomycin–K^+ complex, six 4→1 intramolecular hydrogen bonds form a hydrophobic wall and six ester carbonyl oxygens coordinate to K^+. Isopropyl side chains of the wall are exposed to outer hydrophobic membrane (Fig. 7(a)) [18]. Imanishi and co-workers studied these points and examined the transport properties of the macrocyclic dodecapeptide, cyclo(L-Leu-L-Phe-L-Pro)$_4$ (Fig. 8) [6,19]. In their work, the cyclic dodecapeptide bound to Ba^{2+}, and the conformation of the complex was stabilized by four intramolecular hydrogen bonds; the dodecapeptide did not transport Ba^{2+} across the lipid membrane, however. They stated: "It was a difficult task to have a cation binding



Structure of valinomycin / K^+ complex **Structure of cyclo(Gly-eXX-Gly)$_2$ / Metal complex**

(a) (b)

Fig. 7. Structural comparison of (a) valinomycin (adapted from Ref. [18]) and (b) cyclo(Gly-eXX-Gly)$_2$ in complexation with metal cation.

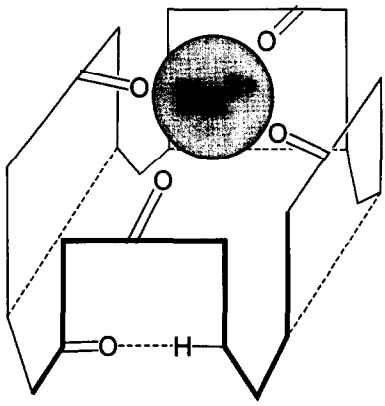


Fig. 8. Schematic drawing of cyclo(L-Leu-L-Phe-L-Pro)$_4$–Ba^{2+} complex (adapted from Ref. [6]).

site correctly suitable at the center of the hydrophobic cyclic peptide only by changing the primary sequence of a large number of amino acid residues". They therefore sought another approach; Sar residues were used as units of a 24-membered cyclic peptide [6,20]. The small steric hindrances of cyclo(Xyz-Sar)$_4$ offered the selective transport for Ca^{2+} through lipid membrane. Nishino et al. reported a 'practical' artificial 18-membered cyclic peptide which showed selectivity for Ca^{2+} (Fig. 9) [21]. Steric hindrance between side chains was employed in this selectivity. Another new type of cyclic peptide, bicyclic peptide (Fig. 10), was synthesized and found to bind to metal cations three-dimensionally like cryptand [22]. The stability constants of these bicycles were enhanced compared with those of monocyclic peptides (Table 1) [23–34]. The introduction of an *N,N'*-ethylene bridge into macrocyclic peptide is

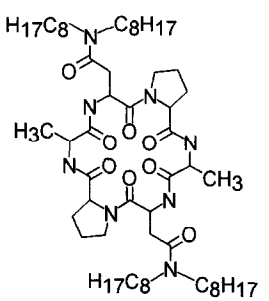


Fig. 9. cyclo(D-Asn(Oct)2-L-Pro-L-Ala)$_2$.

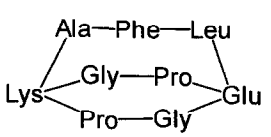


Fig. 10. Cyclo(L-Glu-L-Pro-Gly-L-Lys-L-Pro-Gly)-cyclo(1γ→4ε)-L-Leu-L-Phe-L-Ala.

Table 1
1:1 complex-formation constants (log K_1) of various cyclic peptides

Cyclic peptide	Mg^{2+}	Ca^{2+}	Ba^{2+}	Solvent	Reference
12-membered ring					
cyclo(L-Glu(OMe)-L-Pro)$_2$	1.59	1.75	2.46	95% MeOH	[23]
cyclo(L-Glu-L-Pro)$_2$		1.49	2.44	95% MeOH	[23]
18-membered ring					
cyclo(L-Pro-Gly)$_3$		2.11		Water	[24]
	5.00	5.04		Acetonitrile	
		3.14	2.62	80% MeOH	
cyclo(L-Leu-L-Phe-L-Pro)$_2$		4.02	2.66	Acetonitrile	[25]
cyclo(L-Cys(Acm)-L-Phe-L-Pro)$_2$		5.65	4.10	Acetonitrile	[25]
24-membered ring					
cyclo(L-Pro-Gly)$_4$	0.11	0.49	2.41	Water	[26]
	5.08	5.53	6.20	Acetonitrile	
cyclo(L-Leu-L-Pro)$_4$		Very low	2.62	95% MeOH	[27]
cyclo(L-Lys(Z)-L-Pro)$_4$		2.11	3.11	95% EtOH	[27]
cyclo(Gly-L-Lys(Z)-Sar-L-Pro)$_2$	3.75	3.88	4.43	Acetonitrile	[28]
cyclo(L-Lys(Z)-Sar-L-Leu-Sar-L-Leu-Sar-L-Leu-Sar)	~1.00	4.46		95% MeOH	[29]
cyclo(L-Glu(OMe)-Sar-L-Lys(Z)-Sar-L-Leu-Sar-L-Leu-Sar)	~0.90	4.28		95% MeOH	[29]
cyclo(L-Lys(Z)-Sar-L-Leu-Sar)$_2$	2.08	3.85		95% MeOH	[20]
cyclo(L-Lys(Z)-Sar)$_4$	~1.00	3.72		95% MeOH	[20]
cyclo(Gly-eLL-Gly)$_2$	3.83	6.62	4.69	Acetonitrile	[30]
cyclo(Gly-eVV-Gly)$_2$	4.67	4.76	4.11	Acetonitrile/1,4-dioxane = 4/1	[31]
36-membered ring					
cyclo(L-Leu-L-Phe-L-Pro)$_4$			4.49	Acetonitrile	[19]
Bicycle					
cyclo(L-Glu-L-Leu-L-Pro-Gly-L-Lys-L-Leu-L-Pro-Gly)-cyclo(1γ→5ε)-Gly	6.00	6.00	6.00	Acetonitrile	[32]
cyclo(L-Glu-L-Ala-L-Pro-Gly-L-Lys-L-Ala-L-Pro-Gly)-cyclo(1γ→5ε)-Gly	5.57	7.16	5.40	Acetonitrile	[33]
Valinomycin	<0.7	2.70	3.34	MeOH	[34]

another new approach to hydrophobic ionophores. The structures of macrocyclic pseudopeptides containing *N,N'*-ethylene-bridged dipeptides are similar to the overall structure of valinomycin, except that the intramolecular hydrogen bonds of valinomycin are replaced by covalent bonds (Fig. 7(b)).

3.1. Binding properties of 24-membered cyclic peptides and pseudopeptide toward metal cations

Fig. 11 indicates the relationship between the stability constants (log K_1) of cyclic octapseudopeptide, cyclo(Gly-eLL-Gly)$_2$, and the ionic radii of metal cations [30,35]. The order of log K_1 for bivalent ions of alkaline earth, first transition and Group XII metal cations are $Mg^{2+} < Ca^{2+} > Ba^{2+}$, $Mn^{2+} > Fe^{2+} > Co^{2+} > Ni^{2+} < Cu^{2+} < Zn^{2+}$ and $Zn^{2+} < Cd^{2+} > Hg^{2+}$ respectively. This tendency confirms that this macrocycle prefers a metal cation having an approximate 0.95–1.00 Å radius. This result differs from the order shown in 24-membered cyclic peptides containing Pro residues (the order of stability constants of alkaline earth metal cations with 24-membered cyclic peptides is $Mg^{2+} < Ca^{2+} < Ba^{2+}$ (Table 1)). The order of log K_1 with 18-membered cyclic peptides is the same as that with 24-membered cyclic pseudopeptides containing *N,N'*-ethylene-bridged dipeptides, thus suggesting that the cavity size of 24-membered cyclic pseudopeptide is almost the same as those of 18-membered cyclic peptides. ^{13}C NMR studies of cyclo(Gly-eLL-Gly)$_2$ revealed that six amide oxygens bind to Ca^{2+}, Cu^{2+} and Fe^{2+}, and four bind to Ba^{2+} (Fig. 12). The number of binding points has great influence on stability constants. Contrary to our expectations, this macrocycle rarely transported metal cations through organic liquid membrane.

The authors also prepared *N,N'*-ethylene-bridged N^{ε}-benzyloxy-carbonyl-(*S*)-lysyl-glycine (eK(Z)G) by application of acid catalyzed cyclization (Scheme 4) [36]. It is

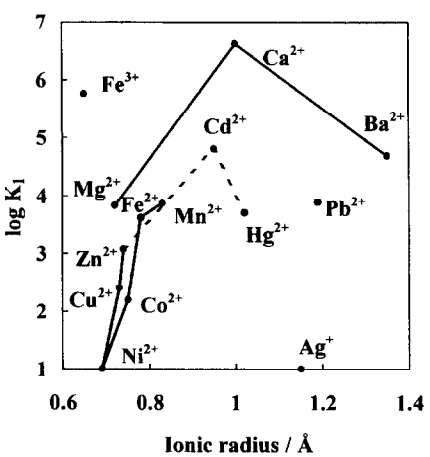


Fig. 11. Relationship between metal ionic radii and the stability constant of metal complex ions with cyclo(Gly-eLL-Gly)$_2$ in acetonitrile.

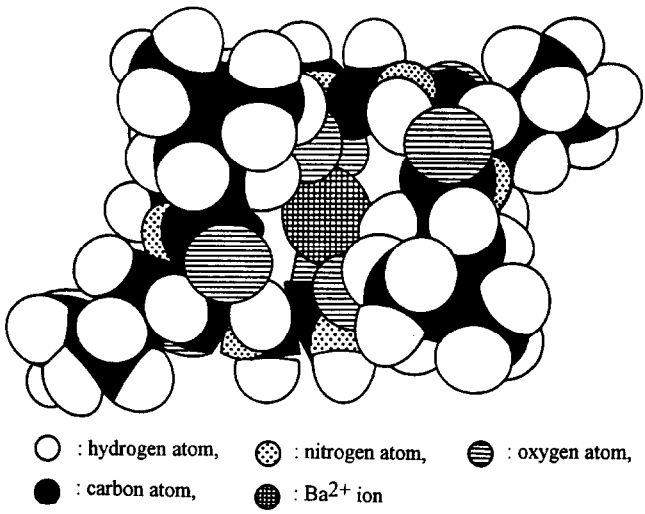
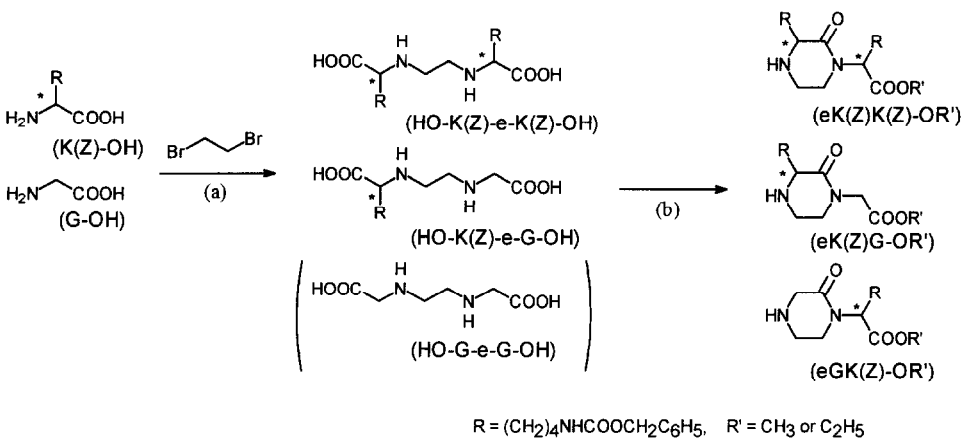


Fig. 12. Proposed structure of cyclo(Gly-eLL-Gly)$_2$–Ba^{2+} complex in acetonitrile (reproduced with permission from Ref. [30]).



Scheme 4. Synthesis of *N,N'*-ethylene-bridged N^{ε}-benzyloxycarbonyl-(*S*)-lysyl-glycine (eK(Z)G): (a) NaOH aq, K_2CO_3 aq, HO–G–e–G–OH removed by washing with hot water; (b) H^+, R'OH.

expected that macrocyclic peptide containing this eK(Z)G unit can offer unique host–guest chemistry. Since the functional donor group can be connected to the side chain of lysine residue, amide oxygens in a macrocyclic skeleton and the introduced functional group can interact with metal cation cooperatively in three-dimensional fashion (Fig. 13). This concept is similar to that of lariat-type crown ether [37], except that ether oxygens are replaced by amide oxygens. The authors have obtained a cyclo(Gly-eLL-Gly-Gly-eK(Boc-(*S*)-His)G-Gly)–Cu(II) complex, showing cooper-

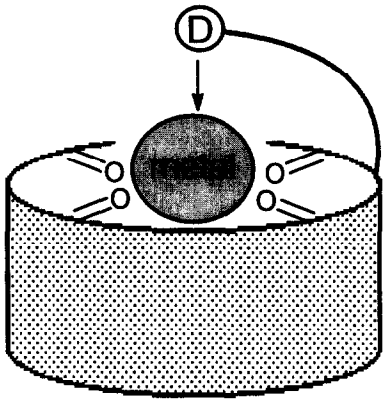


Fig. 13. Schematic drawing of metal complex with armed cyclic pseudopeptide.

ative coordination of amide oxygens and imidazole nitrogens by NMR measurements [38].

4. Macrocyclic peptides as host molecules having chiral recognition properties

In comparison with ionophorous studies of macrocyclic peptides, there are few examples of artificial peptides capable of recognizing amino acid derivatives in an enantioselective fashion. Blout and co-workers indicated the diastereomeric complex formation of cyclo(Gly-Pro)$_4$ with amino acid salts in a four point binding mode using ^{13}C NMR measurements (chemical shifts of amino acid derivative were different between (*R*)- and (*S*)-isomer with macrocyclic peptide) [4,26]. Macrocyclic pseudopeptide containing *N,N'*-ethylene-bridged dipeptides also induced different chemical shifts between (*R*)- and (*S*)-organic ammonium cation [39–42]. For 1-phenylethyl ammonium salt, in particular, cyclo(Gly-eLL)$_4$ showed the greatest distinction in ^{1}H and ^{13}C NMR measurements (Fig. 14) [40]. Recently, the authors and their colleagues discovered that macrocyclic pseudopeptides of this type are excellent enantioselective carriers of racemic amino acid ester salts [43]. Liquid–liquid extraction experiments and transport experiments through organic liquid membrane also showed the highest enantioselectivity of cyclo(Gly-eLL)$_4$ for amino acid derivatives. This proved that the modification of cyclic peptide has overcome its disadvantages and offers a new type of chiral receptor.

5. Conformation analysis of macrocyclic pseudopeptides

Since the peptide bond in *N*-terminal of eXX residue is tertiary amide, the difference of energy between cis–trans configuration is small [44], and this bond rotates at room temperature. NMR measurement showed the presence of cis and trans conformers and their equilibrium [10,11,45]. The assignment of cis and trans configuration

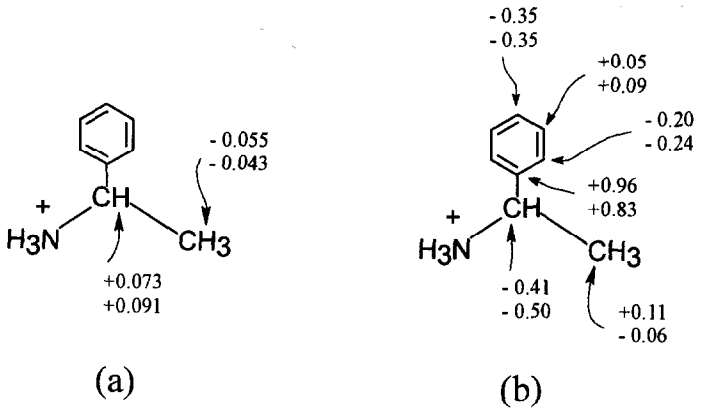


Fig. 14. Induced changes in (a) ^{1}H and (b) ^{13}C NMR chemical shifts (ppm) of 1-phenylethylamine·HBr by cyclo(Gly-eLL)$_4$ in $CDCl_3$: upper, (*R*)-1-phenylethyl amine·HBr; lower, (*S*)-1-phenylethyl amine·HBr; [cyclo(Gly-eLL)$_4$]/[(*R*)-form]/[(*S*)-form] = 0.015/0.010/0.005 mol dm^{-3}.

was based on the chemical shifts of H^2 and H^{4e} and chemical exchange signals on NOESY spectra between these two conformers. Each signal of H^2 in the trans conformer and H^{4e} in the cis conformer was observed at a lower field in comparison with that of H^2 in the cis conformer and H^{4e} in the trans conformer, respectively, because of the magnetic anisotropy effect of the Gly amide carbonyl group (for instance, the chemical shifts of H^2 and H^{4e} in Boc-Gly-eLL-OH are shown in Fig. 15

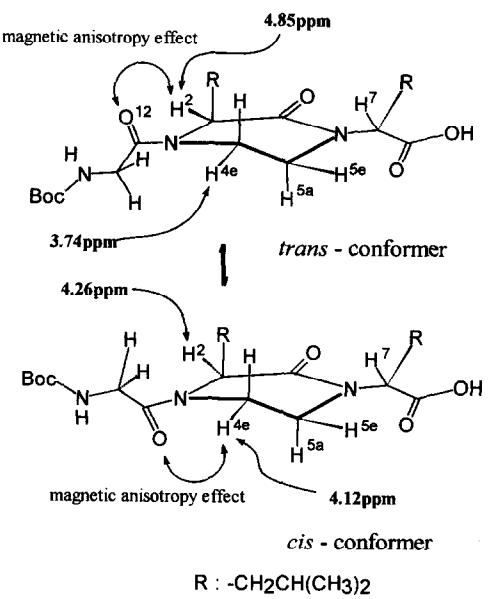


Fig. 15. Equilibrium between two conformers of Boc-Gly-eLL-OH in CD_3CN.

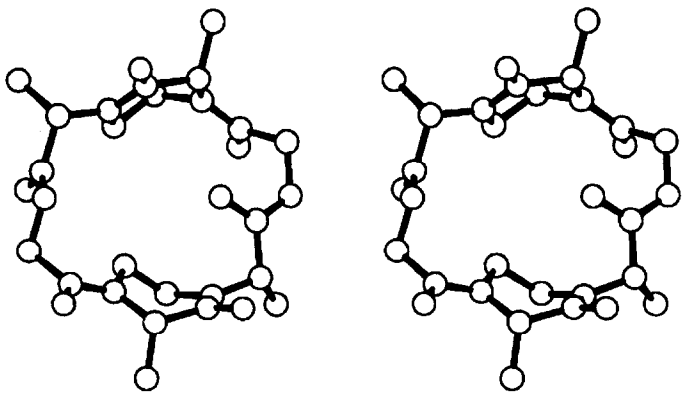


Fig. 16. Stereo view of structure of cyclo(Gly-eAA)$_2$ determined by X-ray crystal analysis.

[41]). It was revealed by these chemical shifts that in major conformers of several cyclic pseudopeptides, all peptide bonds except for Gly-eFF and Sar-eFF bonds are trans in solution [11]. However, solid state conformation of cyclo(Gly-eAA)$_2$ from CH_3CN at room temperature showed the presence of one cis and five trans peptide bonds (Fig. 16) [46]. The peptide bonds of major conformer in this cyclic pseudopeptide are all trans in CD_3CN at low temperature. The fact that the ^1H NMR signal of this molecule is broad at room temperature proved that there is equilibrium of an all-trans conformer, a one-cis–five-trans conformer, etc. in solution, and a one-cis–five-trans conformer separated out in a crystallized condition. This information has important relevance to further molecular design.

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