SYNTHESIS OF MACROBICYCLIC PEPTIDES[1,2]

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Abstract —— With a view to design a new type of host molecules, macrobicyclic peptides in which two lysyl ε-amino groups in cyclic peptides were intramolecularly bridged were synthesized.

The design and synthesis of host compounds remains one of the challenging and stimulating problems of the current organic chemistry, and various host molecules have been reported such as crowns[3], cryptands[4], cyclophanes[5], and cylodextrins[6]. To mimic host-guest complex in nature, hosts that contain rigid cavities must be designed and synthesized. Cyclic peptides, with highly chiral environments and modifiable functionalities in the side chain, may be one of attractive members of host family in the host-guest chemistry, since the conformational flexibility of peptide backbone is considerably reduced from that for open-chain analogs.

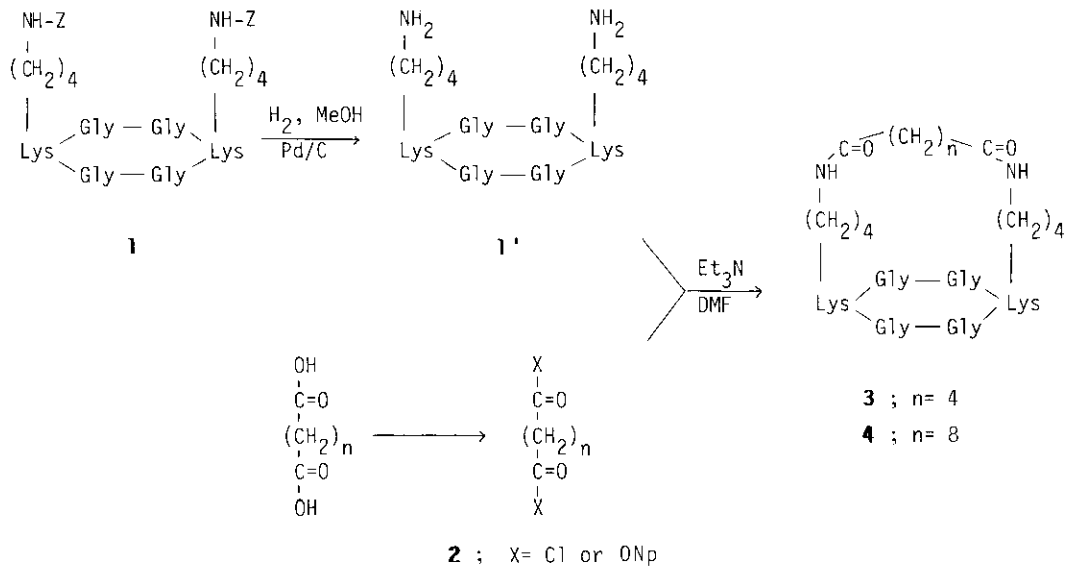
In a previous paper[1], we synthesized a variety of cyclic peptides modified in the amino acid constituents and in the ring sizes, and analyzed their conformational characteristics in solution.

Topologically, macrocycles of type **(A)** define two-dimensional circular cavities. Molecular frame works of higher cyclic order contain three-dimensional cavities. Such is the case for macrobicycles like **(B)** (Chart 1).

(A) **(B)**

Chart 1

In this communication synthesis of macrobicyclic peptides, **3** and **4**, which contain three-dimensional cavities is reported. Cyclo(-Gly-Lys(Z)-Gly-)$_2$, **1**, was synthesized from a linear hexa-peptide, H-(Gly-Lys(Z)-Gly)$_2$-OH as reported[1]. Two lysyl ε-amino groups of **1'** were intramolecularly bridged by adipic acid and sebacic acid to give **3** (n= 4) and **4** (n= 8), respectively. The products were purified through ion exchange chromatography (Scheme 1). Reaction yield at the bridging step is moderately good as shown in Table I.[7] Physical characteristics of **3** and **4** are also shown in Table I.



Scheme 1

Table I Reaction yield at bridging step and physical characteristics of **3** and **4**

Product	Acylating agent **2**	Yield (%)	mp (°C)	$[\alpha]_D$ (c=1,DMF)	FD-MS	Elemental Analysis C	H	N
3	n=4, X=Cl	25	176(dec)	-4.0	594(M^+)	C: 52.51	7.21	18.84
	n=4, X=ONp	30				F: 52.70	7.21	18.76
4	n=8, X=Cl	34	246(dec)	-5.5	650(M^++Na)	C: 55.37	7.74	17.72
	n=8, X=ONp	45				F: 55.19	7.89	17.70

Bridging reaction for the preparation of 3 and **4** with di-p-nitrophenyl adipate or di-p-nitrophenyl sebacate was carried out as follow. A solution of cyclic peptide **1** (55.7 mg, 0.1 mmol) was catalyticaly hydrogenated in 50 % aqueous methanol using Pd/C in the presence of hydrochloric acid. The resulted **1'** hydrochloride and triethylamine (0.3 mmol) was dissolved in DMF (50 ml). To this solution a solution of di-p-nitrophenyl adipate or di-p-nitrophenyl sebacate (0.12 mmol) in THF (10 ml) was added dropwise over the period of 1.5 h at 60°C. The reaction mixture was kept at room temperature overnight. The resulted macrobicyclic peptide was purified passing through Dowex 50 and Dowex 1 columns (2 x 20 cm; medium, 50 % aq. DMF), and recrystallized from acetonitrile-water. In the reaction with adipyl chloride or sebacyl chloride, **1** (55.7 mg, 0.1 mmol) was catalyticaly hydrogenated as described above. The resulted hydrochloride and triethylamine (0.5 mmol) was dissolved in DMF (50 ml). To this solution added a solution of adipyl chloride or sebacyl chloride (0.12 mmol) in THF (10 ml) dropwise during the period of 30 min at room temperature and kept for 12 h. The product was isolated and purified as above.

Quite a few studies on the macrobicyclic peptide have been published. A report by Blout *et al*[8]. is only the case we know. In the report the preparation of a bicyclic nona-peptide in which ε-amino and β-carboxyl groups at a cyclic hexapeptide are linked through tripeptide backbone was described. Preliminary results for the observation of the compound as an ionophore were reported.

Further study to investigate properties of macrobicyclic peptides, 3 and **4** are expected to be informative.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

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2) The amino acid residues mentioned in this paper are of the L-configuration. The abbreviations used to denote amino acid derivatives and peptides are those

recommended by the IUPAC-IUB Commision on Biochemical Nomenclature: Biochemistry, 1972, **11**, 1726. Other abbreviations used: Z= benzyloxycarbonyl, Np= p-nitrophenyl, THF= tetrahydrofuran, DMF= dimethylformamide.

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7) Considerable amount of polymeric products was noticed in the reaction mixture. This suggests that the concentration of **1'** for the bridging reaction (2 mM) is not low enough to avoid possible intermolecular reactions. An attempt to improve the isolation yield is being made under the high-dilution conditions by the simultaneous addition of two reactants by means of a microfeeder.

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