EFFECTIVE SYNTHESES OF CYCLIC PEPTIDES USING A MIXTURE OF ALKALINE METALS AS AN ADJUNCTIVE CYCLIZATION REAGENT

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Cyclic octapeptides (1)-(3) were synthesized from the corresponding linear peptides in satisfactory yields using an equimolar mixture of the alkaline metals LiCl, NaCl, KCl, and CsCl.

KEYWORDS adjunctive cyclization reagent; cyclic peptide; template effect; alkaline metal mixture; cyclization

In a previous paper, we described the preparation of several cyclic peptides and macrocycles containing amino acid residues and examined their abilities to selectively transport amino acid methyl ester and amine salts through a liquid membrane.[2-5] The cyclization of linear peptides is usually achieved in fair yield by a high-dilution method, but sometimes the results are unsatisfactory. Recently, we improved the cyclization yield in the preparation of a 30-membered macrocycle (PPL-30) by adding an alkaline metal ion. A study of the template effect of some alkaline metal ions showed that Cs^+ gave the best result.[3] We have examined further whether cyclization of peptides is promoted by these alkaline metal ions. But for the cyclization of other novel host compounds, like cyclic peptides, macrocycles, and crown ethers, finding the most effective alkaline metal for the template is difficult without intricate preliminary experiments.

To solve this problem, we tried cyclizing linear peptides using an equimolar mixture of LiCl, NaCl, KCl, and CsCl expecting to achieve a general template effect. We were rewarded with good results (Table I). Use of this general reagent should facilitate the preparation of various cyclic host compounds without preliminary experiments.

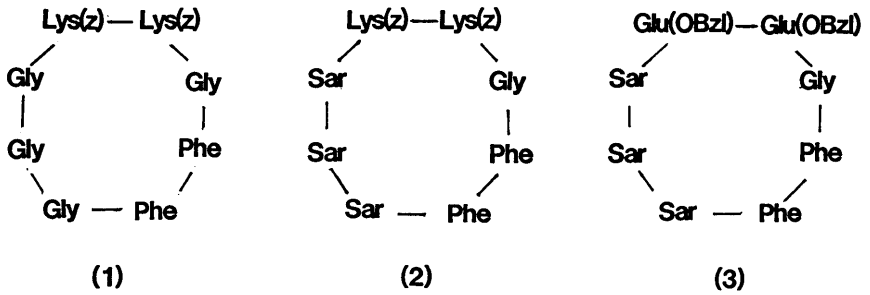

Chart 1. Cyclic Octapeptides (1)-(3)

Cyclic octapeptides (1)-(3) were synthesized by cyclization of the corresponding linear precursors (4), (8), and (9). The linear octapeptide H-$((Lys(Z))_2$-Gly-$(Phe)_2$-$(Gly)_2$-OH·TFA (4) was prepared as described elsewhere.[2] On the other hand, the tripeptide Boc-$(Lys(Z))_2$-Gly-OH (5) and the pentapeptide H-$(Phe)_2$ -$(Sar)_3$ -OMe·TFA (6) were prepared by the CDI or IBCF condensation method. The octapeptide Boc-$(Lys(Z))_2$ -Gly-$(Phe)_2$ -$(Sar)_3$ -OMe (7) was prepared by condensing the tripeptide (5) with the pentapeptide (6) by the EDCI-HOBt procedure. Next, (7) was hydrolyzed with 1 N NaOH in methanol at 40°C, and the Boc group was cleaved by treatment with TFA-anisole to obtain H-$(Lys(Z))_2$

-Gly-$(Phe)_2$ -$(Sar)_3$ -OH·TFA (8). [mp 132-134°C, FAB-MS m/z: 1107$(M+H-TFA)^+$, 973$(M+H-TFA-134)^+$]. H-$(Glu(OBzl))_2$ -Gly-$(Phe)_2$ -$(Sar)_3$ -OH·TFA (9) [mp 119-122°C, FAB-MS m/z: 1021$(M+H-TFA)^+$] was synthesized in a stepwise manner starting with H-$(Phe)_2$-$(Sar)_3$-OH·TFA by the IBCF condensation method, followed by Boc deprotection with TFA-anisole.

Linear octapeptides (4), (8), and (9) were cyclized by the EDCI-HOBt method. The respective linear octapeptide, N-methylmorpholine, and HOBt were dissolved in anhydrous DMF. The solution was added dropwise to a mixture of EDCI·HCl, the equimolar of the alkaline metals (10 eq.), anhydrous THF and DMF over a period of 5 h at room temperature. The reaction mixture was stirred for 10 days at room temperature. The solvent was evaporated in vacuo and then ethyl acetate was added to the residue. This solution was washed with 10% sodium bicarbonate, cold 1 N HCl and water, then dried over magnesium sulfate and evaporated to dryness. The crude product was purified by column chromatography on silica gel. The eluent with chloroform/methanol (95:5) afforded cyclic octapeptide. (2) glassy solid (mp 122-124°C), Rf = 0.67 (chloroform:methanol:water = 8:3:1), $[\alpha]_D^{27}$ = -13.2° (C = 1, methanol), FAB-MS m/z: 1089$(M+H)^+$, 955$(M+H-134)^+$. Anal. Calcd for $C_{57}H_{72}N_{10}O_{12}\cdot 2H_2O$: C, 60.84; H, 6.81; N, 12.45. Found: C, 61.01; H, 6.63; N, 12.16. (3) glassy solid (mp 114-116°C), Rf = 0.69 (chloroform:methanol:water = 8:3:1), $[\alpha]_D^{27}$ = -11.8° (C = 1, methanol), FAB-MS m/z: 1003$(M+H)^+$, 913$(M+H-90)^+$. Anal. Calcd for $C_{53}H_{62}N_8O_{12}\cdot H_2O$: C, 62.34; H, 6.31; N, 10.97. Found: C, 62.60; H, 6.24; N, 10.92. Spectral data for the cyclic octapeptide (1) agreed with previously reported data.[2]

Table I. Yields of Cyclic Octapeptides Using the Equimolar Mixture of the Alkaline Metals[a]

Compounds	Concentration of linear peptide in cyclization (mM)	Isolation Yield (%) Mixture of the alkaline metals not used	used
(1)	0.6	58	72
(2)	1.2	14	41
(3)	1.2	15	46

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

Table I shows that the isolation yields of cyclic octapeptides (1)-(3) significantly increase when an equimolar mixture of alkaline metals is used for the cyclization.

REFERENCES AND NOTES

1) Amino acids and peptide derivatives mentioned in this paper are of the L-configuration. The following abbreviations are used: Sar = sarcosine, Boc = t-butoxycarbonyl, Z = benzyloxycarbonyl, TFA = trifluoroacetic acid, CDI = N, N'-carbonyldiimidazole, IBCF = isobutylchloroformate, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = N-hydroxybenzotriazole, DMF = N, N-dimethylformamide, THF = tetrahydrofuran.

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