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SYNTHESIS, CONFORMATION AND ION-COMPLEXING PROPERTIES OF CYCLO-[L-Tyr(OBzl)-Gly]$_3$

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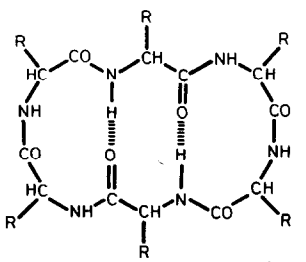
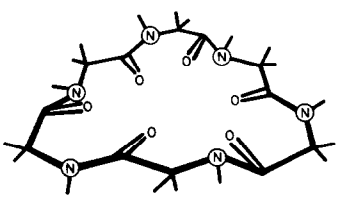
The hydrogen-bonded conformation (1) exhibited by simple cyclic hexapeptides[1] can be used to explain the lack of ion-complexing properties in these 18-membered ring compounds. These compounds contrast with the cyclodepsipeptides of similar ring size in the enniatin series[2] which cannot form transannular H-bonds because of their N-methylamide-ester backbone structure. However, the cyclic hexapeptide,[3] cyclo-(L-Pro-Gly)$_3$ shows ion-complexing characteristics which has been explained in terms of its ability to adopt a symmetric conformation (2) which allows the CO groups to complex in a very analogous manner to the enniatin B series. Thus both the enniatins and the above cyclic hexapeptide appear to achieve their complexing properties by modifying the H-bonding characteristics of (1).



(1)



(2)

It seemed plausible that a cyclic hexapeptide containing suitable side-chains in the correct configurational relationship, which could sterically interact with one another to destabilise the conformational form (1) and favour (2) could give rise to ion-complexation. The availability of protected tyrosyl peptides from an independent study[4] facilitated the synthesis of cyclo-[L-Tyr(OBzl)-Gly]$_3$ (3) as a model compound. The glycine residues function as the D-residues to maintain the LDLDLD configuration, while it was speculated that the bulky aromatic side-chains in O-benzyltyrosyl residues would compete for

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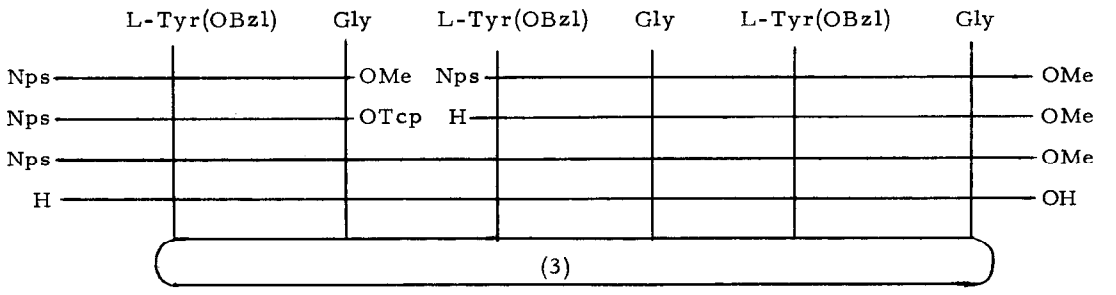
the space on one side of the cyclopeptide ring system in an analogous way to cyclo-(L-Tyr-L-Tyr),[5] a feature which interferes with the conformation of the cyclodipeptide ring. The nett result might be the favouring of the form (2), or at least reduce the stabilisation of the H-bonded form (1).

Cyclic peptide (3) was synthesised according to the Scheme. Cyclisation of the linear precursor was achieved in 55% yield by the chlorophosphite method,[6] using o-phenylene chlorophosphite and a 50% excess of imidazole.

SCHEME



Cyclic peptide (3) m.p. 286-288°C (dec.) (Found: C, 68.26; H, 5.51; N, 8.65%. $C_{54}H_{54}N_6O_9.H_2O$ requires C, 68.35; H, 5.69; N, 8.86) did not give a M^+ ion (theoretical M, 930) using electron impact mass spectrometry, but a molecular ion at 1014 ($M^+ + 6CH_2$) was obtained on N-methylation using the Hakamori method. A cluster of peaks at 931 ($M^+ + H$), 932 ($M^+ + 2H$) in a field-desorption mass spectrum* gave added evidence for the authenticity of the compound.

The ion-complexing properties of the cyclopeptide (3) relative to well-known complexing agents was assessed using an ion-selective electrode[7] (kindly measured for us by Ulla Fiedler at the University of Lund, Sweden). The results are recorded in the Table. It can be concluded from the slope characteristics mV/pK that the cyclopeptide probably acts as a K^+-complexing agent although the selectivity versus sodium is poor.

An ability to complex is further confirmed by the changes in the N-H region of the pmr spectrum, when K^+SCN^- is added to the cyclopeptide (3) in d_6DMSO solution. The two, broad, equally intense peaks at δ (ppm) 8.0 and 8.2 coalesce into one peak at δ8.1 (KSCN : cyclopeptide ≃ 1 : 2) suggesting that a symmetrical complex is formed.

Application of the full range of physico-chemical methodology[8] in determining the conformation of the cyclopeptide, has been restricted by the low solubility of the cyclopeptide in solvents other than DMSO. Nevertheless, some interesting deductions

* Kindly obtained from Varian AG, Zug, Switzerland.

can be made. A proton-decoupled ^{13}C n.m.r. spectrum (25.2 MHz) showed a particularly simple set of signals:[(a)] (ppm, with TMS as internal standard), 171.01, 168.77 (CO); 156.91, 137.12, 130.00, 129.91, 128.31, 127.58, 114.44 (aromatic carbons); 69.09 (OCH_2); 54.64 (Tyr C_α); 42.5 (Gly C_α); 35.78 (Tyr C_β). The simplicity of this spectrum supports a symmetrical structure, with no evidence of an asymmetric form as found for cyclo(Pro-Gly)$_3$ in DMSO.[3]

TABLE

K^+-selectrode Membrane, PVC+	Slope mV/pK			pK_{KNa}	
	H_2O	0.01M NaCl	0.1M NaCl	0.01M Na^+	0.10M Na^+
DOA (dioctyladipate)	47.8	18.1	18.9	0.75	1.51
DOA + valinomycin	59.5	58.1	56.2	2.19	3.75
DOA + dicyclohexyl-18-crown-6	53.4	42.1	28.8	2.31	2.48
DOA + cyclopeptide (3)	37.8	12.8	5.1	0.66	1.02

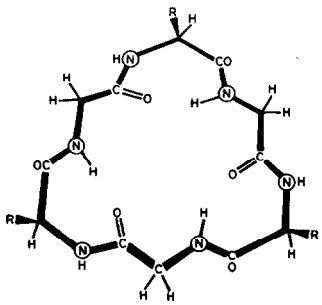
The ^{13}C spectrum of (3) containing the added KSCN [KSCN : (3), ≈1 : 2] in d_6DMSO shows only one small change in the spectrum - a 0.1 ppm downfield shift of the CO carbons at 168.77 ppm. Although this is small it does imply some interaction with only three of the carbonyl groups in the cyclohexapeptide.

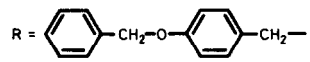
Although the signals in the ^1H n.m.r. (100 MHz) spectrum are too broad for a detailed conformational study, the two equally intense signals for the N-H protons (δ ppm 8.0 and 8.2), also support a symmetrical conformation. A temperature coefficient[8] ($\Delta\delta/\Delta T$) of 4 x 10^{-3} ppm/°C for both these signals falls in between the range for strong intramolecular H-bonds (0-2 x 10^{-3}) and highly solvated bonds (6-12 x 10^{-3}). The N-H signals underwent slow D_2O exchange at ambient temperature (much faster at 80°C).

The i.r. spectrum (KBr) showed an intense N-H peak at 3275 cm^{-1} (bonded N-H) with broad, but very much weaker shoulder peaks at 3380 and 3450, while the amide CO absorbed at 1635 cm^{-1} (shoulder peak 1655).

Our data, together with a study of molecular models suggest that the cyclopeptide (3) could exist in DMSO as a symmetrical structure (4) containing relatively weak internal H-bonds, possible of the 1→3 type, which could allow it to adopt a more symmetrical conformation of type (2) when complexing. At this stage of our study we cannot predict the conformation of the side chains.

(a) Correlation based on comparison with ^{13}C spectrum of Gly-Tyr(OBzl)OEt and published data.[5a]





(4)

This, therefore, represents a similar conformation to the S-form[3] of cyclo-(Pro-Gly)$_3$ or that predicted[9] for cyclo(Val-Sar)$_3$. Our data indicate that the cyclopeptide is only a weak complexing agent yet as far as we can ascertain, cyclopeptide (3) is the first example of a cyclohexapeptide with all secondary amide bonds which is capable of ion-complexation.

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