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SPECTROSCOPIC STUDIES OF CYCLODIPEPTIDES CONTAINING PIPECOLIC ACID, PROLINE AND/OR 2-AZETIDINECARBOXYLIC ACID

K. Bláha, M. Buděšínský, I. Frič, J. Smolíková and J. Vičar
Institute of Organic Chemistry and Biochemistry
Czechoslovak Academy of Sciences, Prague

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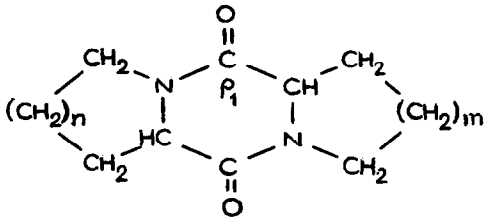
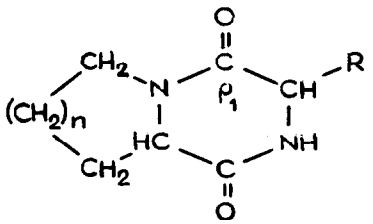
The non-planar nature of the amide bond has recently been subjected to intensive study in relation to the detailed structure of peptide molecules[1]. In the course of systematic studies of the physical properties of peptides in this Laboratory[2] we prepared a series of cyclodipeptides (2,5-piperazinediones) I and II, containing residues of pipecolic acid (Pip), proline (Pro) and/ or 2-azetidinecarboxylic acid (Aze). These polycyclic molecules have a relatively rigid spatial arrangement, so that they can be used as models for the study of the relation of spectroscopic properties to geometric parameters. A recent study by Siemion[3] prompted us to publish salient part of our results as a preliminary communication.



I, n = O (Aze), I (Pro), 2 (Pip);
m = O (Aze), I (Pro), 2 (Pip)
(cis and trans, only cis for n=m=O)



II, n = O (Aze), I (Pro), 2 (Pip);
R = H, i-C_4H_9, $CH_2C_6H_5$
(except R=H cis and trans)

The cyclodipeptides were prepared from linear dipeptides obtained using dicyclohexylcarbodiimide (linear peptides containing 2-azetidinecarboxylic acid using 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline[4]). All the prepared cyclodipeptides showed a satisfactory elemental analysis and mass-spectrometric fragmentation.

In the entire series we measured infrared (IR), proton magnetic resonance (PMR) and circular dichroism spectra (CD). The results were interpreted in relation to the

probable conformations derived from inspection of Dreiding models and symmetry considerations. The geometric parameters (conformation of the central ring, valence angles ρ_1 and torsion angle at the amide bonds ω) in this series are changed by anelation (cis or trans) of one or two additional rings (4-, 5- and/or 6-membered) to the central 2,5-piperazinedione ring.

The PMR spectra (see Table 1) confirmed our stereochemical concepts. The equivalence of both glycine C_α-H protons, the low value of $J_{\alpha H,NH}$ and the marked difference in the chemical shift of C_ω-H of the Pip residue show that in c(Gly-Pip) the 2,5-piperazinedione ring is nearly planar. In c(Gly-Pro), and even more in c(Gly-Aze), the equivalence of the glycine C_α-H protons disappear; a difference in $J_{\alpha H,NH}$ and very similar chemical shifts of both C_ω-H protons suggest a boat conformation of the 2,5-piperazinedione ring. Of the tricyclic compounds both c(Pip-Pip) have practically the same spectra, showing a very similar (planar) conformation of the central ring and its immediate environment. On the other hand, the PMR spectra of diastereoisomeric c(Pro-Pro) show marked differences suggesting varied conformations: in the cis-isomer a deep boat, and even deeper in cis-c(Aze-Aze), in the trans-isomer planar conformation.

TABLE 1 PMR Data of Some Cyclodipeptides Containing Pip, Pro, and/or Aze[a]

Compound	Chemical shift and coupling constants			
	C_α-H[b]		C_ω-H[b]	
c(Gly-Pip)	4.02 t, $J_{\alpha N}$=1	3.84bd	-	2.52bt; 4.69bd
c(Gly-Pro)	3.86dd, $J_{\alpha N}$=4.0; 4.10bd, $J_{\alpha N} \leqslant 1$	4.11bt	-	3.58m
c(Gly-Aze)	3.73dd, $J_{\alpha N}$=5.0; 4.06bd, $J_{\alpha N} \leqslant 0.5$	4.95bt	-	4.13t
cis-c(Pip-Pip)	3.81 bd		2.50bt; 4.68bd	
trans-c(Pip-Pip)	3.82bd		2.50bt; 4.69bd	
cis-c(Pro-Pro)	4.20bt		3.53dd	
trans-c(Pro-Pro)	4.08bt		3.30m; 3.96m	
cis-c(Aze-Aze)	4.98bt		4.10m	

[a]All PMR spectra were measured in $CDCl_3$ (TMS as internal reference). Chemical shifts are given in δ-scale (ppm) and coupling constants $J_{\alpha H,NH}$ in Hz. Presented data are limited to C_α-H and C_ω-H only. [b]Data for the first amino-acid residue are in the first column.

In the IR spectra the wavelength of characteristic ν(CO) bands increases in the order: c(Pip-Pip) [cis 1662.4, trans 1663.4 cm^{-1}] < c(Pro-Pip) [cis 1668.7, trans 1669.4 cm^{-1}] < c(Pro-Pro) [cis 1676.8, trans 1670.8 cm^{-1}] < c(Aze-Aze) [cis 1690.0 cm^{-1}]. Differences between the trans-isomers reflect primarily a decrease in the valence angle of the carbonyl group (ρ_1), a further shift to higher wavelengths is caused by the non-planar arrangement of the amide bond in cis-c(Pro-Pro) and particularly in cis-c(Aze-Aze). ν(CN) bands were detected in the spectrum by means of the solvent shift ($\Delta = \nu_{CHCl_3} - \nu_{CCl_4}$). In compounds with a planar or very shallow boat configuration of the central ring the ν(CN) vibration participates in several bands owing to coupling with the scissoring vibrations of CH_2 groups (in CCl_4 1450-1460 cm^{-1}, Δ = +5 cm^{-1}). In compounds with a pronounced boat conformation the ν(CN) vibration becomes characteristic, with a band below 1430 cm^{-1} which is markedly solvent sensitive [cis-c(Pro-Pip) 1425, Δ = +18 cm^{-1}; cis-c(Pro-Pro) 1420, Δ = +15 cm^{-1}; cis-c(Aze-Aze) 1396.8 cm^{-1}, Δ = +19 cm^{-1}. The characteristic of the ν(CN) vibrations results from the changed geometry of the central ring and from mutual interaction of both amide bonds. A shift to lower wavelengths in cis-isomers is given by the increasing non-planarity of the amide bonds; shifts of ν(CO) and ν(CN) can be correlated in this regard.

According to the relation of the signs of the $\pi - \pi^*$ bands in the CD spectra to the absolute configuration of the amino-acid residues one can differentiate two subgroups of compounds: a) Pip derivatives in which the signs of the $\pi - \pi^*$ and $n-\pi^*$ bands are the same as those of monocyclic dipeptides[5] with aliphatic side chains. Both types of cyclodipeptides apparently have the same boat chirality. b) Pro and Aze derivatives have opposite signs of the $\pi - \pi^*$ bands than compounds under a) and therefore should have also an enantiomeric boat chirality (for L-residue characterized by angles $\phi < 180^\circ$, $\psi > 180^\circ$). In Pip derivatives the steric requirements are approximately the same as in aliphatic monocyclic dipeptides, the amide bond is distorted only slightly from planarity (if at all). In Pro and Aze derivatives the deformations of the central ring are of more pronounced nature with a greater degree of non-planarity, as judged by the shift of the $n-\pi^*$ band in cis-c(Aze-Aze) and detection of a second bathochrome band in cis-c(Pro-Pro) in hexafluoroacetone (233 nm). Non-planarity of the amide bond affects the transition energy and the chiroptical properties can be different from systems with planar amide bonds.

TABLE 2 CD Data : λ_{max} and $[\theta]$

c(D-Pip-Gly)	216.5 (+14 300)		193.5 (-26 700)
c(L-Pro-Gly)	213 (+18 000)		187.5 (-81 000)
c(D-Aze-Gly)	230.5 (+2 200);	206.5 (-16 700)	189 (+23 200)
c(D-Pip-D-Pip)	212 (+34 500)		195 (-73 000)
c(L-Pro-L-Pro)	219.5 (+12000);	203 (+9 900)	185 (-40 000)[a]
c(D-Aze-D-Aze)	226.5 (+24700);	207 (-36 500)	185 (+17 000)[a]

[a]End value.

In summary, trans-dianeled cyclodipeptides have their 2,5-piperazinedione rings very close to planarity or planar. In monoaneled and cis-dianeled compounds this ring assumes essentially a boat conformation the depth of which increases with decreasing size of the aneled ring. In the same manner anelation contributes to non-planarity of the amide bond.

Full papers will be published in Collection Czechoslovak Chem. Communications.

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