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CIRCULAR DICHROISM CURVES, INFRA RED SPECTRA AND DIPOLE MOMENTS OF DIASTEREOMERIC CYCLOHEXAALANYLS*

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In a previous communication (2) we have described NMR-studies of a series of cyclic hexapeptides in polar solvents (dimethylsulfoxide, water). The present work was aimed at elucidating their conformational states in non-polar solvents. Diastereomeric cyclohexaalanyls I - III (Fig. 1) were chosen for the investigation, the solubility of other cyclic hexapeptides being inadequate for quantitative physicochemical measurements.

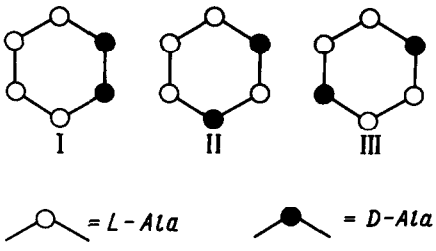

Fig. 1. Diastereomeric cyclohexaalanyls I - III

The NMR-studies revealed the cyclohexapeptides to be in a conformational equilibrium in which the "pleated sheet" conformation first proposed by Schwyzer (3) is predominant. The CD-curves of this conformer are characterized by week $n \rightarrow \pi^*$ Cotton effects at 210-230 nm and two strong effects of opposite sign at 205-180 nm, associated with the split $\pi \rightarrow \pi^*$ transition of amide groups (4).

With less polar solvents (ethanol-heptane, 1:2) the number, signs and positions of the Cotton effects do not change, although their intensities are somewhat redistributed (Fig. 2). The data obtained give grounds to assume that in non-polar solvents cyclic peptides retain the overall structural type

*For details see (1)

and 4 ⟶1 intramolecular hydrogen bonds (IHB) but that other conformers with somewhat different Φ and Ψ co-ordinates and probably with some additional IHB are favoured.

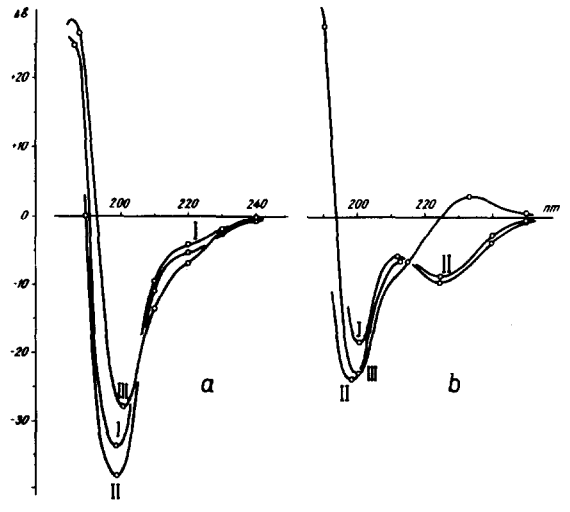

Fig. 2. CD-curves of compounds I - III in water (a) and ethanol-heptane, 1:2 (b)

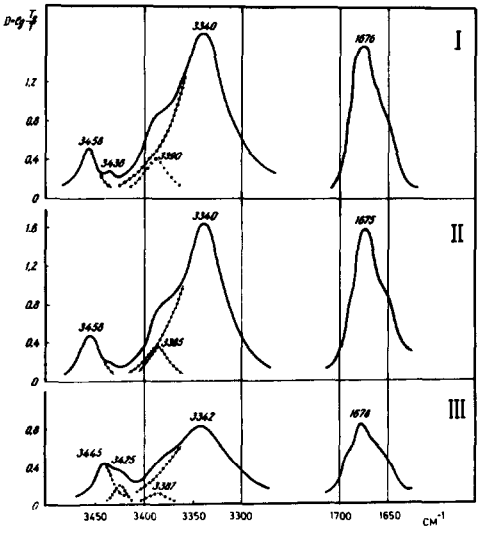

Fig. 3. IR-spectra of compounds I - III in chloroform

This assumption was confirmed by an IR-study of compounds I - III in dilute ($5 \cdot 10^{-4}$ mole/l) $CHCl_3$ solutions. As seen from Fig. 3 each spectrum shows an intense band in the amide A region (3250-3480 cm^{-1}) with a maximum at 3340 cm^{-1}. There are also several bands at 3410-3460 cm^{-1}. In the amide I region an asymmetric band with a maximum at 1670-1675 cm^{-1} was observed which could not be resolved. Basing on the detailed analysis of the IR-spectra of model amides and peptides (5-8) we assigned the 3340 cm^{-1} bands to the amide NH-groups participating in IHB; bands at 3410-3460 cm^{-1} to different free NH-groups*. Evaluation of the number of NH-groups from the integral intensities A of the respective bonds according to the A-ν_{NH} correlation[1] has shown the cyclic hexapeptides I - III to contain no less that 3 or 4 IHB.

The planar trans-configuration of the amide bonds in the cyclic peptides permits the following possible IHB in addition to the 4 ⟶1 type present in

*French authors (7) have assigned the 3420 cm^{-1} bands to NH-groups forming 1 ⟶1 IHB. However, this assignment, inconsistent with the energy computations, does not appear to be sufficiently well founded (8).

the "pleated sheet" model (Fig. 4).

A: between the 2 and 5 NH-groups and the 6 and 3 carbonyls.

B: between the 3 and 6 NH-groups and the 1 and 4 carbonyls.

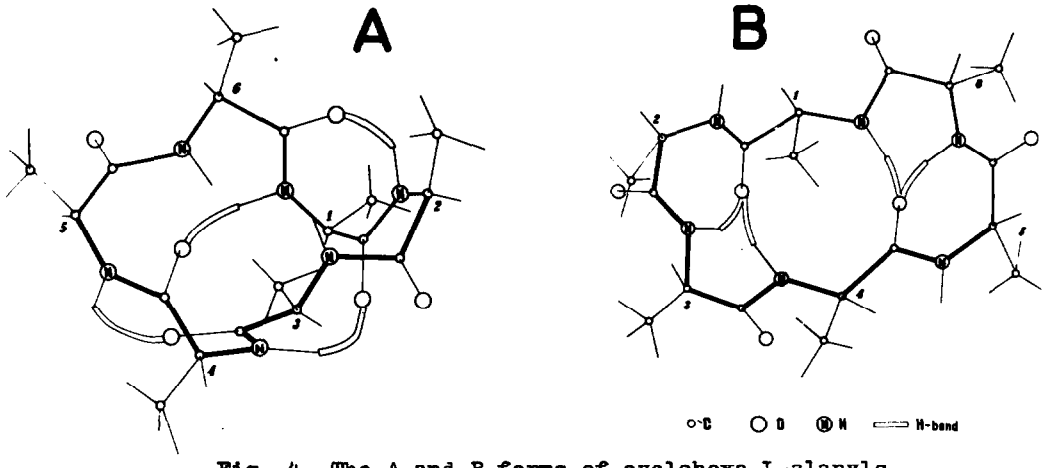

Fig. 4. The A and B forms of cyclohexa-L-alanyls

Both A and B forms contain 3→1 type of IHB, stabilizing seven membered rings. It has been shown (5-8) that amide groups involved in such bonding give IR bonds at 3340-3390 cm^{-1} in good agreement with the spectra we have obtained for compounds I - III (Fig. 3).

The participation of one amide carbonyl simultaneously in two IHB has as yet not been observed in peptides; however, energy computations show that such structures would have low local potential energy minima (9).

Further information on the structure of compounds I - III was obtained by comparing theim dipole moments measured in $CHCl_3$ with those calculated for the A and B forms (Table 1). The calculation was made by stepwise summation of the amide dipole moment vectors along the peptide chain in a given conformation. The range of Φ and Ψ values for the A and B forms was estimated from molecular models and relevant theoretical studies (9-12). The data presented

TABLE 1

Experimental dipole moments of cyclohexaalanyls I - III in $CHCl_3$ (μ , D)			Calculated dipole moments of A and B forms of cyclohexapeptides (μ , D)	
I	II	III	Form A	Form B
4.4 ± 0.8	5.0 ± 0.3	5.9 ± 0.3	1.0 - 8.0	5.7 - 8.0

in Table 1 show that although form A is more preferable a certain amount of form B could also be present, the low intensity IR band at 3385 cm^{-1} being ascribable to its unusual 3→1 IHB.

It follows from the above said that cyclic hexapeptides in non-polar media have a rather rigid structure consisting of condensed 10-membered and 7-membered rings stabilized by 4→1 and 3→1 IHB. It is noteworthy that an analogous IHB system was recently found in Na^+ complex of a biologically important cyclopeptide antamanide (13). Its IR-spectrum in the amide A region is similar to the spectra of cyclic hexapeptides.

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