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CONFORMATION OF CYCLO[PRO-PHE-GLY-PHE-GLY] [1)]

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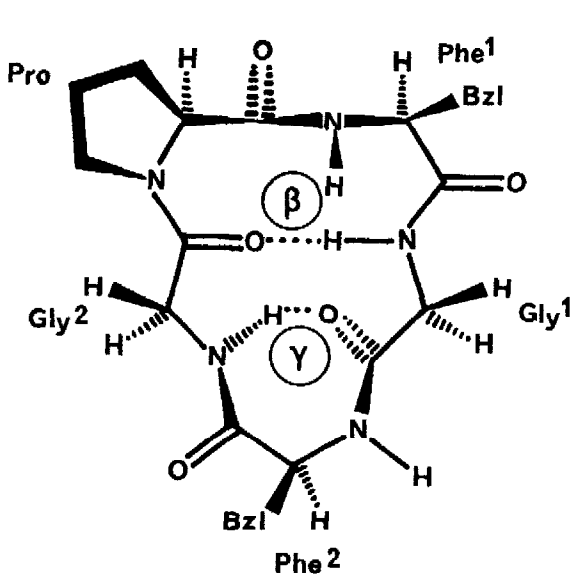
Pentapeptides are considered to be smallest cyclic peptides which allow a trans conformation of all amide bonds without deformation to a great extent[2)]. Although much is known about the conformation of cyclic tetra- and hexapeptides[3)], there is very little information about cyclic pentapeptides[4,5)]. We assume that conformational mobility of the latter causes a fast equilibration between several conformations with respect to the NMR time scale. Such an equilibrium is degenerate in the case of homopeptides[6)]. In cyclopentapeptides containing more than one kind of amino acid there should be one or more conformation, which can differ in population, in the equilibrium. In some cases only one of the possible conformations dominates, and it is possible to determine which this is from NMR spectra in the usual way (temperature dependence of NH-signals[3b)], TFE-induced shifts[7,12)], and coupling constants[3b,8)]).

In this paper we report that cyclo[Pro-Phe-Gly-Phe-Gly] populates pre-

dominantly one conformation as can be proved by the following results:

1. ^{13}C-NMR-spectra unequivocally show that the main conformation has a trans proline peptide bond[9] (C^{γ}=24.6 ppm in $CDCl_3$; 24.5 ppm in DMSO).
2. The temperature dependence of the amide protons in DMSO shows that both Gly-NH groups are shielded from the solvent (small temperature coefficients, $\Delta\delta/T$) while the Phe-NH groups (larger values of $\Delta\delta/T$) are in agreement with these facts. Inspection of molecular models (Dreiding and CPK models) show that both of these conformations are possible.



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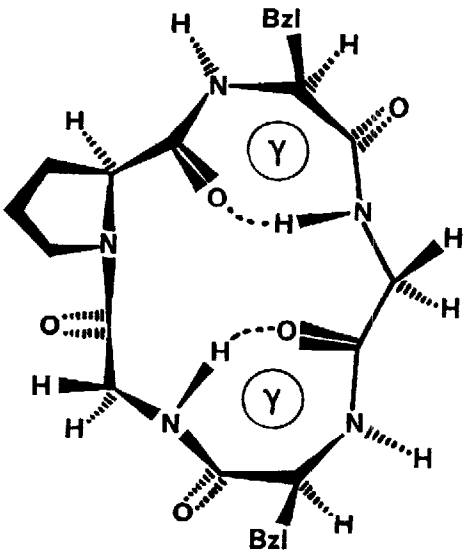

II

3. The spectra in DMSO and $CDCl_3$ confirm these results: in $CDCl_3$ the Phe-NH-signals are shifted strongly upfield by the loss of hydrogen bonds to the solvent, whereas the glycine resonances are less affected[12] (see Table).

4. The addition of trifluoroethanol (TFE) induces downfield shifts in the amide-proton signals Phe^B, Gly^A, and Gly^B [13] (see Table). This is caused by the hydrogen bond of TFE to the adjacent solvent-exposed carbonyl groups of Pro, Phe^1, and Phe^2 in conformation I[13] (see Figure). In conformation II one expects both Phe-NH signals to shift to high field because both adjacent CO-groups are intramolecularly hydrogen bonded.

   This different behaviour with TFE therefore allows the assignment of the Phe-NH signals of the spectrum to the Phe in the sequence ($Phe^A \rightarrow Phe^2$, $Phe^B \rightarrow Phe^1$).

Consequently we suggest that the title compound possesses the conformation I which involves one β-loop and one γ-loop. Additional support to this conclusion arises from the well known preference[3a] that Pro apparently shows for occupying that position in the β-loop of peptides.

Table: ^{1}H-NMR-Results of NH-Chemical Shifts.

signal	δ [ppm] $CDCl_3$ [a]	δ [ppm] DMSO [b]	$\Delta\delta/T$ [c] DMSO	presence of hydrogen bond to solvent	TFE induced shift [d]	nature of neighbouring CO-group
Phe^A	6.61	7.56	4.3	yes	-2.1	bound
Phe^B	6.97	8.26	7.3	yes	+0.4	free
Gly^A	7.37	7.68	1.7	no	+0.8	free
Gly^B	7.58	7.74	1.7	no	+1.4	free

a) at 43°C; b) at 46°C; c) in 10^{-3} ppm/K; d) in Hz/10% TFE.

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(8) Because of the large difference of rates it is inadequate to apply H-D exchange in such cases. This can cause incorrect interpretations by the contribution of minor populated conformations in fast equilibrium[3b,5b].

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(13) Notation Phe^{A}, Phe^{B}, etc. refers to the signals in the NMR spectrum; Phe^{1}, Phe^{2}, etc. to the sequence of the peptide.