Unique Conformation of the Cyclic Octapeptide of Sarcosine and a Related Depsipeptide

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Summary Cyclo-octasarcosyl has the *cis,cis,trans,trans,-cis,cis,trans,trans*-conformation both in the crystal and in solution.

FROM the presence of four equally intense *N*-methyl lines in the 60 MHz n.m.r. spectrum of cyclo-octasarcosyl $[N(Me)–CH_2–CO]_8$ it was concluded[1] that only one of the thirty-eight possible *cis,trans*-isomers is present in $CHCl_3$ solution and that it has the configuration sequence *cis,cis,-trans,trans,cis,cis,trans,trans*. Although it was then overlooked that two of the other isomers (*ccctccct* and *ctttcttt*) would also satisfy the spectrum, we now present evidence that the configuration sequence is that proposed both in the crystal and in solution.

The 100 MHz n.m.r. spectrum of cyclo-octasarcosyl at $-10°$ strengthens the earlier conclusion of conformational homogeneity, since the higher resolution fails to reveal additional *N*-methyl lines and also shows just four CH_2 quartets (two widely split with $J = 16$ and 17 Hz, and two narrow with $J = 18$ Hz). This is also the conformation in the solid since the i.r. spectrum in the transparent regions of a $CHCl_3$ solution (low solubility in CCl_4) is identical with that of the solid in KBr.

The crystal structure of cyclo-octasarcosyl was determined on crystals which were grown from methanol solution, but nevertheless turned out to be a tetrahydrate. The crystals belong to the orthorhombic system with space group *Pbca*, $a = 18{\cdot}340$; $b = 18{\cdot}279$; $c = 18{\cdot}875$ Å; $Z = 8$. About 5000 independent reflections, of which 3500 were used in the analysis, were measured on an automatic four-circle diffractometer, and the structure was solved by direct methods.[2] At the present stage the structure has been refined by full-matrix least-squares to an *R*-value of *ca.* 7%. It is shown in the Figure as viewed along [001].

The ring conformation is surprisingly open with the inner volume filled by a cluster of four water molecules, which participate in a network of inter- as well as intra-molecular hydrogen-bond bridges. Each of the four pairs of diametrically placed amino-acid residues is related by an approximate two-fold axis. There are no direct transannular interactions to be held responsible, as originally thought,[1] for the uniqueness and rigidity of this ring conformation, which persists in $CHCl_3$ solution where no water

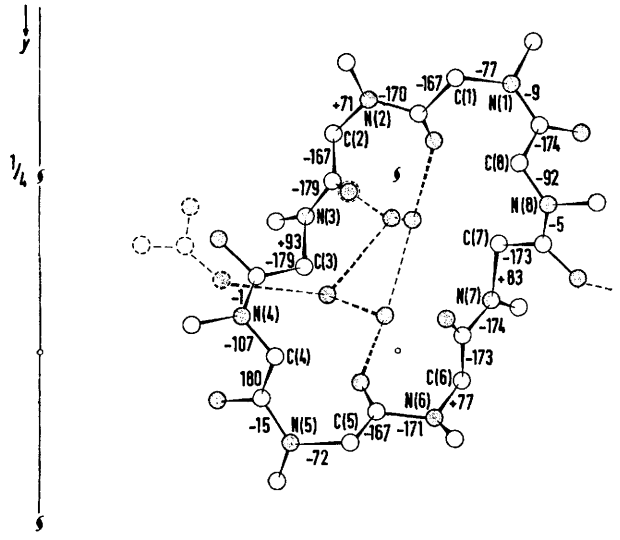

FIGURE. *Crystal structure of cyclo-octasarcosyl tetrahydrate. Open circles are carbon atoms, filled circles nitrogen (marked) or oxygen atoms. Dihedral angles refer to the ring skeleton.*

molecules are present to form transannular bridges. The explanation must therefore be sought in the intrinsic conformation of the peptide chain itself. It is then of particular interest that the dihedral angles of all C–C(α) bonds lie in the narrow range 167—180° (Figure), in excellent agreement with the large observed value for all four geminal coupling constants, adopting the theoretical relationship between the value for this coupling constant and the orientation of the CH_2 group with respect to the C=O bond.[3] In cyclotetrasarcosyl[4] the C–C(α) dihedral angle is either 170 or 66°; thus, it seems that this bond has a normal *gauche,anti*-situation. For the N–C(α) bonds the dihedral angles lie in the wider range 71—107° (Figure); hence, this bond is somewhat less defined and follows no *anti,gauche* pattern (*cf.* 94 and 121° for cyclotetrasarcosyl[4]). The most striking feature, however, is that each of the two *trans*-amide ring portions [from C(1) to N(4) and from C(5) to N(8)] forms part of a right-handed helix with a threefold screw axis and a translation of *ca.* 3·1 Å, which is practically identical with the polymer helix observed for polyglycine II[5] and for poly-L-proline II,[6] and that each of the two *cis*-amide ring portions [from C(3) to N(6) and from C(1) to N(2)] forms part of a right-handed helix with a translation of 2·3 Å, which resembles the polymer helix proposed for poly-L-proline I.[7]

A corresponding cyclo-octadepsipeptide having two glycolic acid residues in diametric positions, cyclo(Sar_3–OGl–Sar_3–OGl), m.p. 295°, was obtained in a doubling reaction on cyclization of H–Sar_3–OGl–OTcp in pyridine. Its 'low-temperature' n.m.r. spectrum is interpretable on the basis of exactly the same ring conformation, assuming that one pair of *trans*-amide groups has been replaced by a pair of *trans*-ester groups. In fact, the only differences from the cyclo-octasarcosyl spectrum are that just one *N*Me line is lacking (which constitutes an additional proof that diametrically placed groups are equivalent), that the 16 Hz CH_2– quartet is replaced by a 15 Hz quartet at lower field, and that coalescence starts at a lower temperature (0 *vs.* 40°). Furthermore, no differences are observed between the i.r. spectra of the solid and of a $CHCl_3$ solution, so that the crystal conformation must also in this case be the same.

Cyclo-octasarcosyl forms a complex with KNCS. Its n.m.r. spectrum is very different from that of the uncomplexed ring, thus proving that the ring conformation has changed on complexation. We have not been able to demonstrate complex formation with the depsipeptide.

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