Crystal and Solution Conformation of Cyclopentasarcosyl

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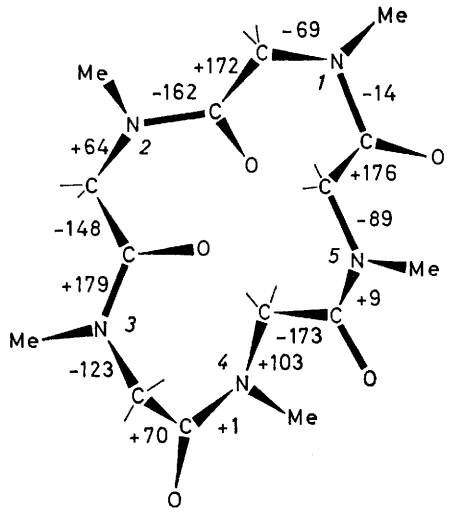
Summary The *cis,cis,cis,trans,trans*-conformation found for cyclopentasarcosyl in the crystal is also predominant in solution, whereas many other cyclic pentapeptides are conformer mixtures in solution.

THE n.m.r. spectrum of cyclopentasarcosyl [N(Me)–CH_2–CO]$_5$ at room temperature shows five equally intense *N*-methyl lines and five CH_2 quartets, from which it has already[1] been concluded that the $CDCl_3$ solution contains one dominant conformer and that this cannot have only *cis*- or only *trans*-amide groups. Some weak additional *N*-methyl lines can be assigned to a second conformer present to less than 10%. When crystals are dissolved in $CDCl_3$ at −50°, the n.m.r. spectrum at this temperature is essentially the same, except that the extra lines are absent; they appear quickly, however, at −20°. Since *cis-trans* isomerization is expected[2] to be fast at −20°, this shows that the crystal conformer is identical with the dominant solution

conformer. The usual correlation of solid and solution by i.r. spectroscopy was inconclusive in this case.



FIGURE

The crystal structure of cyclopentasarcosyl was determined on crystals grown from methanol, but actually found to be a dihydrate. The crystals belong to the monoclinic system with space group $P2_1/c$, $a = 9{\cdot}31_6$; $b = 30{\cdot}15_4$; $c = 7{\cdot}81_8$ Å; $\beta = 113{\cdot}7°$; $Z = 4$. The phase problem was solved by direct methods, and the R-value arrived at for 2298 of the 3800 reflections measured on an automatic four-circle diffractometer was 7·6%. The water molecules participate in a network of intermolecular hydrogen-bond bridges involving only two of the amide oxygen atoms (residues 1 and 3). The projection of the cyclic pentapeptide shown in the Figure has been chosen so as to allow direct comparison with the earlier projection of the cyclo-octasarcosyl molecule.[3] Quite unexpectedly, the ring contains a succession of three *cis*-amide groups and another succession of two *trans*-amide groups. Three amide groups deviate significantly from planarity. Of the dihedral angles in the C–C_α bonds, at least four follow the *anti–gauche* pattern observed for cyclotetrasarcosyl[4] and cyclo-octasarcosyl.[3] There is again excellent agreement between the n.m.r. geminal coupling constants observed in solution and the orientation of the CH_2 group with respect to the C=O bond observed in the crystal; thus, three of the quartets are narrow and have large J values (18 Hz) and correspond to the three clear *anti*-bonds, while two are widely split and have small J values (14 and 15 Hz) and correspond to the bonds with 70 and 148° dihedral angles, respectively. The N–C_α bonds have dihedral angles varying from 64 to 123°, and again this is as observed in the peptides mentioned.

The most striking feature is the resemblance of this cyclic pentapeptide conformation with the corresponding cyclic octapeptide conformation.[3] In fact, if the ring is cut open in the *gauche* C–C_α bond of sarcosine residue 3, and the two ends spread somewhat apart, the whole chain (residues 3,2,1,5,4) becomes in every detail identical with a part of the octapeptide ring skeleton (residues 3,2,1,8,7). Some features are also reminiscent of the conformation of the two 16-membered lactonic pentapeptide rings of crystalline actinomycin.[5]

The conformational homogeneity of cyclopentasarcosyl is in contrast with the heterogeneity of a series of cyclic pentapeptides containing both sarcosine and glycine or alanine, where the crystal conformer is not dominant and may not even be present in solution. As an example, cycloglycyltetrasarcosyl when dissolved at −75° in $CHFCl_2$ shows one set of n.m.r. lines, including four sharp N-methyl lines; at −40° a new set of lines due to a second conformer develops, which finally is completely replaced by a third set belonging to the dominant solution conformer. An analogous situation exists for cycloalanyltetrasarcosyl, and here the final equilibrium contains also the second conformer but no crystal conformer is left.

A similar replacement of sarcosine residues in cyclic tetrapeptides does not generally lead to conformer mixtures.[6]

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