Cyclic Oligopeptides of Sarcosine (*N*-Methylglycine)

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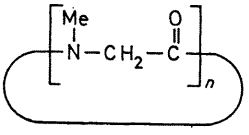
CYCLIC oligopeptides of common α-amino-acids having a primary amino-group are known and present challenging conformational problems. Thus, a strong tendency for the formation of cyclic hexapeptides, instead of tripeptides, has been observed,[1] but it is still unclear whether transannular hydrogen bonding is a factor stabilizing particular conformations of such ring structures.

As hydrogen bonding is excluded when the amino-group carries a methyl substituent, it might be expected that cyclic oligomers of sarcosine should reveal more clearly the unperturbed ring conformation. A higher lipophilicity should also make dipole moment measurements and spectral studies in solution easier. On the other hand, due to the similarity between $-CH_3$ and $-CH_2-$, the strong *trans*-preference for the amide group should disappear on *N*-methylation, and a cyclic tripeptide, hitherto only reported[2] for the rather special five-ring amino-acid proline, might become available. The free competition between the *cis*- and *trans*-amide configuration in rings less constrained than the cyclic dipeptide might also yield information about the intrinsic conformation of the *cis*-amide group (planar or skew) and even of the *trans*-amide group (*N*-methyl in or out of the plane of the other atoms).

We now report the synthesis of six cyclic oligopeptides of sarcosine of the general formula (I). Cyclodisarcosyl, or *NN'*-dimethyldiketopiperazine ($n = 2$) is formed with extreme ease directly from sarcosine 2,4,5-trichlorophenyl ester and is also encountered as a by-product in the syntheses of the higher homologues. Cyclotrisarcosyl ($n = 3$), cyclotetrasarcosyl ($n = 4$), and cyclopentasarcosyl ($n = 5$) were prepared by cyclization of the corresponding linear oligopeptides, disarcosyl-, trisarcosyl-, and tetrasarcosyl-sarcosine obtained by stepwise synthesis. In all steps the benzyloxycarbonyl blocking group was used on the amino end, the methyl ester on the carboxyl end, and



(I) $n = 2,3,4,5,6,8$

dicyclohexylcarbodi-imide as condensing agent. Conversion of the methyl ester to the 2,4,5-trichlorophenyl ester,[3] using again carbodi-imide, was followed by removal of the benzyloxycarbonyl group by catalytic hydrogenation, and cyclization in pyridine at high dilution. After passage through an ion-exchange column, the cyclic products were sublimed. Together with the cyclic tri- and tetra-peptides the doubling products cyclohexasarcosyl ($n = 6$) and cyclo-octasarcosyl ($n = 8$) were also obtained.

Yields in the cyclization step and various properties of the cyclic peptides are compared in the Table.

The n.m.r. spectra (Figure 1) are exceptionally informative and reveal an unexpected configurational (*cis,trans*) and conformational homogeneity even for the largest of these rings.

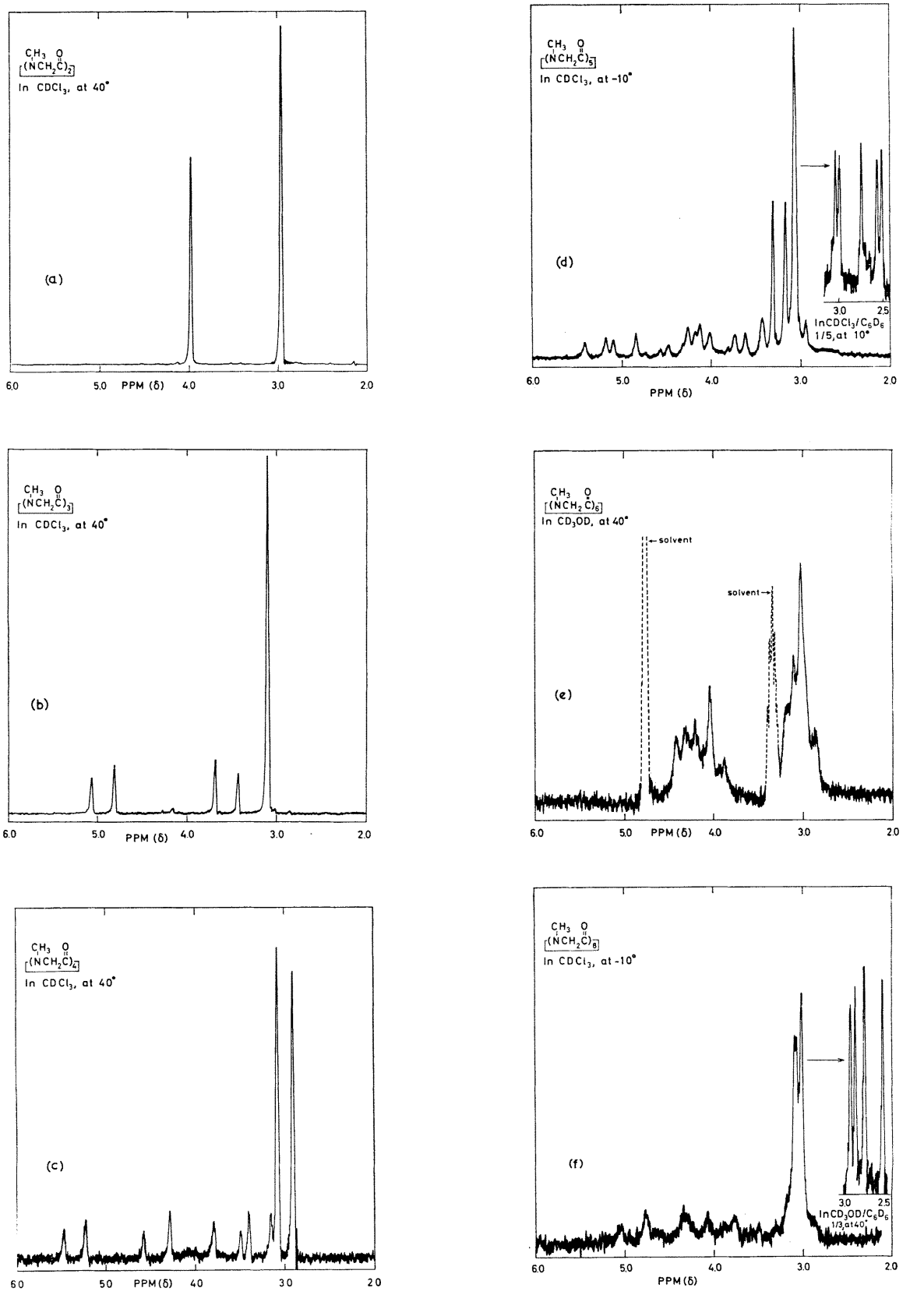

CH3 O
[(NCH2C)2]
In CDCl3, at 40°
(a)
6.0 5.0 PPM (δ) 4.0 3.0 2.0
CH3 O
[(NCH2C)5]
In CDCl3, at -10°
(d)
3.0 2.5
In CDCl3/C6D6
1/5, at 10°
6.0 5.0 4.0 3.0 2.0
PPM (δ)
CH3 O
[(NCH2C)3]
In CDCl3, at 40°
(b)
6.0 5.0 PPM (δ) 4.0 3.0 2.0
CH3 O
[(NCH2C)6]
In CD3OD, at 40°
solvent
solvent
(e)
6.0 5.0 PPM (δ) 4.0 3.0 2.0
CH3 O
[(NCH2C)4]
In CDCl3, at 40°
(c)
6.0 5.0 PPM (δ) 4.0 3.0 2.0
CH3 O
[(NCH2C)8]
In CDCl3, at -10°
(f)
3.0 2.5
In CD3OD/C6D6
1/3, at 40°
6.0 5.0 4.0 3.0 2.0
PPM (δ)

FIGURE 1

TABLE

(I) n =	2 (ref. 6)	3	4	5	6	8	Polysarcosine
Yield in cycl. step (%)		16	43	11	25	5	
Sublim. temp. at 0·01 mm. Hg. ..	100°	150°	200°	240°	270°	300°	
M.p.	147°	221°	>350°	~265°	~300°	328°	>350°
Mol. ion in mass spectrum	142	213	284	355	426	568	
C=O str. freq. i.r. (cm.$^{-1}$) in $CHCl_3$	1670	1650	1670, 1650	1675, 1640	1670, 1645[a]	1675(1650)	1650[a]

[a] In KBr.

Least information is obtained for *cyclodisarcosyl*, whose simple two-line spectrum and lack of coalescence phenomenon indicates either a planar or rapidly inverting nonplanar conformation. A slightly nonplanar conformation is suggested by the dipole moment of 1·13 D observed in benzene solution.†

For *cyclotrisarcosyl* the presence of one singlet for *N*-methyl and one quartet for CH_2, intensity 9 : 6, shows that all amide groups have the same configuration, and since they cannot all be *trans* in a nine-membered ring, they must all be *cis*. The very large splitting of the CH_2 signals means that the ring is far from planar, and the high coalescence temperature of around 135° that it is very rigid. The only conformation that satisfies these data is that of Figure 2 with all carbonyl groups on the same side. It is

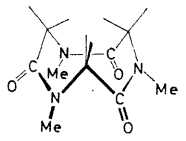


FIGURE 2

to some extent confirmed by the high dipole moment of 4·66 D observed in benzene solution.

Cyclotetrasarcosyl shows two *N*-methyl signals, intensity 6 : 6, and two CH_2 quartets, intensity 4 : 4, which means that out of the six possible isomers there can be only one present. For symmetry reasons the configuration of the four amide groups must have the sequence *cis,trans,cis,trans* and the molecular conformation must be centrosymmetric. All lines start to broaden at 155° and end up as two single lines (CH_2 and NCH_3) at about 200°. Apparently, the two coalescence phenomena expected, collapse of each quartet into one line due to rapid ring inversion, and the further collapse of the two CH_2 lines, as well as the two *N*-methyl signals, into one line due to rapid interchange of amide configuration, occur in the same temperature range. The high temperature needed for coalescence to occur shows that inversion of this nonplanar twelve-membered ring is remarkably difficult. Together with the configurational homogeneity, this suggests strong transannular attractions between at least two amide groups. Since hydrogen bonding is excluded, we suggest that contributions of transannular polar resonance structures (Figure 3) have to be considered as an alternative to the common polar resonance structures $^{-}\cdot OC:\overset{+}{N}<$. The case is reminiscent of the transannular interaction observed by Leonard[4] between an amino- and a keto-group in certain medium rings. An unusually short transannular contact between the ester oxygen and the ketone carbon has been found[5] in the related ten-membered-ring lactone of 9-hydroxy-6-oxononanoic acid.

Cyclopentasarcosyl shows five *N*-methyl lines, intensity 3 : 3 : 3 : 3 : 3, and five recognizable CH_2 quartets, intensity 2 : 2 : 2 : 2 : 2. Some overlap occurs, but involves different lines in the various solvent combinations. The observed integral intensity ratio means that even this fifteen-membered ring is present as one largely predominant isomer out of the eight possible ones, but symmetry arguments can only decide that it is not the all-*cis* or the all-*trans* isomer. Coalescence of the five CH_2-quartets into five singlets, as ring inversion becomes fast enough, starts at about 40°, but is not finished before also the *N*-methyl lines start to broaden at 70°, as configuration interchange becomes fast enough. At 130° only two singlets (CH_2 and NCH_3) are present. Again, the high resistance to ring inversion and the configurational and conformational homogeneity suggest strong transannular interactions between amide groups.

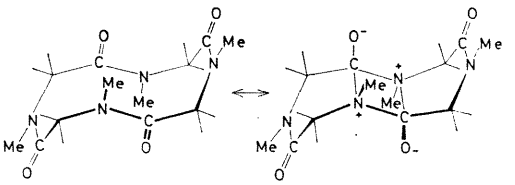


FIGURE 3

Cyclohexasarcosyl, on the other hand, has an n.m.r. spectrum from which no certain conclusions can be drawn as concerns configuration sequence or even number of isomers present (fourteen are possible here). This is in striking contrast to the situation for cyclic peptides of the normal α-amino-acids, where the hexapeptide seems particularly favoured and conformationally best defined.[1] Both the *N*-methyl and CH_2 lines undergo coalescence between 50 and 100° (configuration interchange) but no broadening of the CH_2 signals is observed down to −50°.

Cyclo-octasarcosyl shows four *N*-methyl signals, intensity 6 : 6 : 6 : 6, more or less resolved in various solvent systems. At about 100° coalescence into one *N*-CH_3 line (as well as into one CH_2 line) is observed. By symmetry arguments, an integral intensity ratio of only four *N*-CH_3 lines would indicate that a single isomer out of the thirty-eight possible ones is present, that its configuration sequence is *cis, cis, trans, trans, cis, cis, trans, trans*, and that its conformation has a centre of symmetry. From the CH_2 signals the

† The crystal structure of cyclodisarcosyl has now been determined by Mr. Per Groth (to be published in *Acta Chem. Scand.*) and reveals an extremely flattened chair form. Each amide group contains the *N*-methyl carbon, but not its *N*-CH_2 carbon, in the common plane (dihedral angle CCNC = 7°). Some of the higher oligomers are also being examined by *X*-ray methods.

conclusions are less clear, but in no contradiction. The overlapping unresolved quartets coalesce at 20—40° into two broad lines. It is clear that ring inversion is slow even for this twenty-four-membered macrocycle, and postulation of transannular interactions seems unavoidable.

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[3] J. Pless and R. A. Boissonnas, *Helv. Chim. Acta*, 1963, **46**, 1609.
[4] N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *J. Amer. Chem. Soc.*, 1958, **80**, 4858.
[5] W Fedeli and J. D. Dunitz, *Helv. Chim. Acta*, 1968, **51**, 445.
[6] S. M. McElvain and P. M. Laughton, *J. Amer. Chem. Soc.*, 1951, **73**, 448.