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A MACROCYCLE CONTAINING TWO BIPHENYL AND TWO ALANINE SUBUNITS, SYNTHESIS AND CONFORMATION IN SOLUTION

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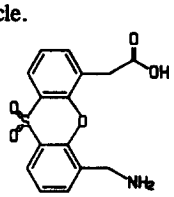
Abstract: The synthesis and solution conformation of the macrocycle cyclo(-2-Ala)$_2$ 3 is presented. The compound 3 contains two alanine and two molecules of the novel pseudoamino acid 2-aminomethyl-2'-carboxymethylbiphenyl 2 in the ring. A phthalimido-protected derivative of 2 is obtained in three steps from diphenic anhydride. The compound 2 is coupled to H-AlaOCH$_3$ and the resulting "dipeptide" dimerizes at the conditions of an azide coupling to 3 (20%). The macrocycle 3 exists in three diastereomeric forms 3A, 3B and 3C which can be separated by HPLC. The form with R,S configuration of the biphenyl groups has C_1 symmetry (3C). The one- and two-dimensional ^{1}H-NMR data of 3C support a structure where the biphenyl groups are orientated in an orthogonal arrangement. One alanine is in an equatorial C_7 conformation, the other alanine is part of a stretched peptide chain. The forms 3A and 3B with C_2 symmetry exist probably as equilibrating structures in solution. The NMR data can be explained with ß-sheet conformations as well as with more bent structures containing γ-loops.

Introduction

The restriction of conformations of peptides can be achieved by different approaches. One method uses cyclic peptides with special amino acid composition leading, for example, to cyclic analogues of peptides of pharmaceutical interest with enhanced activity[1]. A second approach restricts the conformational freedom of peptides incorporating bridges which are derived from natural fragments - e.g. disulphide bridges[2], a modified ß-turn dipeptide[3] or methylene bridges[4].

An alternative way is the incorporation of non-peptide parts commonly used in organic host guest chemistry to build rigid hosts with enforced cavities. First examples of this combination are found with dihydropyridines[5], phenoxathiines[6], thiophenes[7] and bipyridine[8]. Here we report for the first time the synthesis and conformation of a cyclopeptide with two biphenyl units in the peptide ring.

Our initial goal was to develop a new aromatic analogue of a ß-loop forming dipeptide as in ref. 3 and 6. The 2,2'-substituted biphenyl 2 provides in models the right distance for two antiparallel attached peptide chains to build a ß-sheet as proposed for the unit[6] 1. A first molecule which may demonstrate this function is compound 3 in which two biphenyl units 2 and two alanine are incorporated in a cycle.



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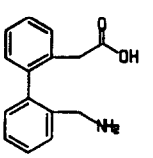

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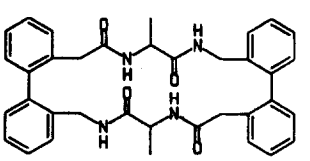
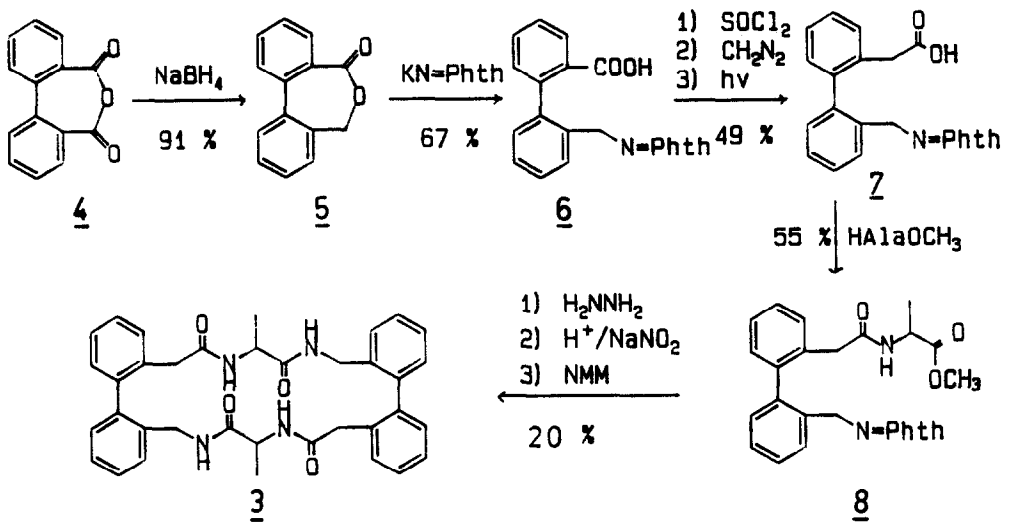


3

Compound 3 may adopt a "ß-loop" conformation (as indicated in the drawing above) and is thus comparable to a cyclic hexapeptide. However, the biphenyl groups are chiral and can epimerize at elevated temperatures, so we expect a complex conformational behaviour of 3.

Synthesis

Our approach to a N-protected derivative 7 of the functionalized biphenyl 1 is shown in Scheme 1. Sodium borohydride reduction[9] of anhydride 4 yields lactone 5, which is then opened to the 2-phthalimidomethyl-2'-carboxy-biphenyl 6. The chain elongation of 6 to give 7 is achieved by a photochemical Arndt-Eistert reaction (total yield 20% over four steps from 4).



4 5 6 7 8 3

Scheme 1

In the subsequent transformations of Scheme 1, propylphoshonic anhydride[10] is used for the peptide coupling reaction. The phthalimido-protection group is removed and the alanine-ester is converted to the hydrazide by treatment with hydrazine hydrate. The azide cyclisation of the resulting hydrazide (2-AlaNHNH$_2$) 9 according to Medzihradszky[11] gives 3 in low yields (20% starting from 8). The dimeric nature of 3 follows from the DCI mass spectrum (see Experimental Part).

A linear precursor of 3 containing both biphenyl groups was also prepared (without full characterization of each intermediate) but the overall yield of 3 after cyclisation was only 6% (starting from 7) and this synthetic route was not studied further.

The HPLC purification of the crude cyclisation material on silica gel with chloroform/acetone gives two fractions obviously containing the two atropisomers 3A and 3C. They interconvert slowly in solution at room temperature (see below). A third isomer 3B precipitates (together with 3A) after

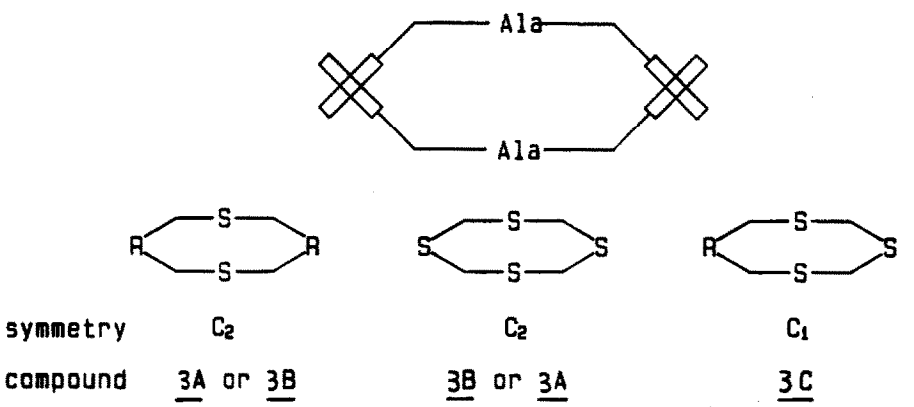
acetone treatment of either the crude reaction product or the 3A, 3C mixture. The equilibration in dimethyl sulfoxide gives 3A, 3B and 3C in a 1/1/2 ratio independent of the starting composition of the mixture.

Conformations of 3

Three forms of 3 are found experimentally. Two of them, 3A and 3C, exist in equilibrium in chloroform, the third form, 3B, is found in addition in dimethyl sulfoxide (see above). The equilibration of 3A to a one to two mixture of 3A and 3C in chloroform (followed by NMR) has a half life of 4 days at 23°C, so the barrier of interconversion is about 25 kcal/mol. Such a high barrier is most probably not due to a cis-trans isomerisation at peptide bonds or to other conformational processes involving single bonds in the peptide backbone. The atropisomerisation of the biphenyl units must be responsible for the long lifetime of the observed conformers.

Two chiral biphenyl groups can be combined with two S-alanine in different ways in the cyclic molecule 3 (Scheme 2). Three diastereomeric forms are expected, two of them with C_2 symmetry and one with C_1 symmetry.

Configurations of cyclo(-2-Ala)$_2$, 3:



symmetry	C_2	C_2	C_1
compound	3A or 3B	3B or 3A	3C

Scheme 2

The NMR spectra of 3A, 3B and 3C in Figure 1 clearly show that 3A and 3B have time averaged C_2 symmetry whereas 3C has C_1 symmetry. Therefore, the two biphenyls in 3C have R and S configuration, respectively. Both biphenyl groups within one of the C_2 forms 3A and 3B have obviously identical configuration (R or S).

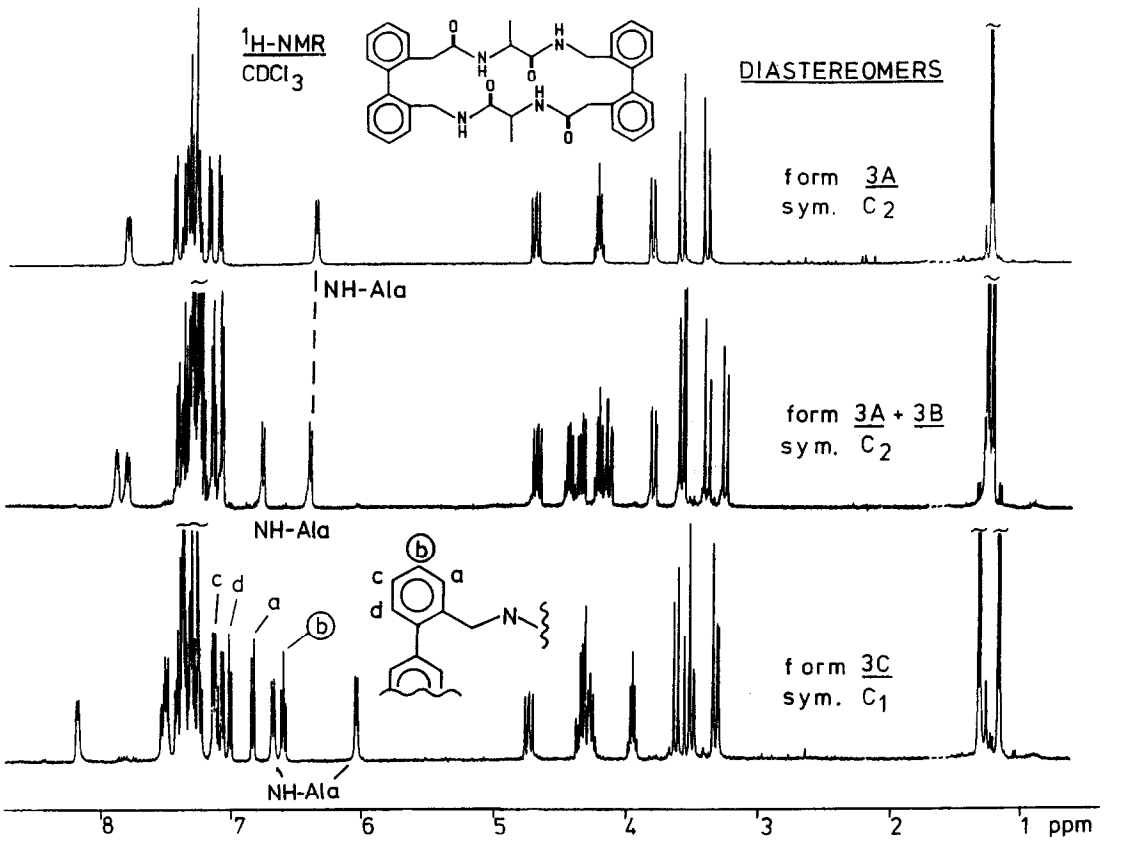


Figure 1: 400MHz ^{1}H-NMR spectra of the diasteromers 3A, 3B and 3C of 3 in $CDCl_3$ at 23 °C. The assignment of the NH-protons of Ala is given for comparison. The protons of one phenyl ring in 3C (marked with letters) are located at relativly high field, see the discussion in the text.

Conformation of the C_1 form 3C

The basis of every conformational discussion by NMR is the correct assignment of the NMR signals. The assignment of the aliphatic and NH signals in the proton spectra of 3A and 3B is straightforward from COSY experiments. The spectrum of 3C (C_1 symmetry) is somewhat more complicated because two different peptide chains (denoted as α and ß) have to be assigned. Each chain consists of an AB system (CH_2-CO), an AMX_3 system (NHCHCH$_3$, Ala) and an ABX system (NHCH$_2$, biphen.). The subsystems are not connected by large scalar coupling constants and only NMR techniques based on small long range coupling constants may be used for sequencing (e.g. homonuclear: COSY for long

range coupling[13], heteronuclear: COLOC[12]). As an alternative method, we used the NOE connectivities within the peptide chains (see Figure 2).

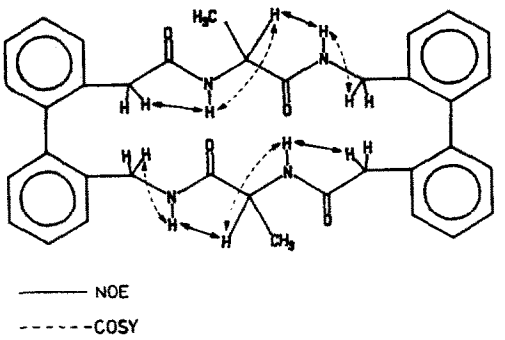
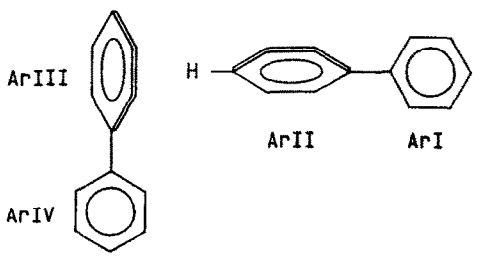


Figure 2: COSY- and strong NOE-connections used in the assignment of the two different peptide chains of 3C.

Obviously, the assignment based on Figure 2 can be wrong if an NOE connectivity between the two chains exists. In the present case however, this requires that at least two of the observed NOE's are cross chain connections between pairs of similar protons (one weak cross chain NOE, not contained in Figure 2, is present, see below). In addition, the proposed spatial arrangement of the biphenyl groups in 3C (s. below) rules out strong interchain NOE's.

A striking observation in the ^{1}H-NMR spectrum of 3C in chloroform is the chemical shift of one set of aromatic ring protons (between 6.6 and 7.1 ppm). For example the proton at 6.6 ppm ("b" in Figure 1) is found between 7.1 and 7.5 ppm in the remaining three aromatic rings. We explain this phenomenon assuming a "edge to face" arrangement of the biphenyl subunits as in Scheme 3. The protons of one ring should be shifted upfield due to the strong shielding effect of the benzene ring current.



Scheme 3

The arrangement in Scheme 3 requires different conformations within the two peptide chains. One chain is elongated, the other has a bent conformation (for example a γ -loop). Long range COSY experiments[14] and NOESY spectra indicate that the upfield shifted aromatic ring is connected to the N-terminus of chain ß. Hence, chain ß has to be the more folded one.

With this information at hand, we started to build a model structure of 3C and refined it by force field calculations using a modified MMP2 program[15]. The result is shown in Figure 3. Chain ß has a C_7 conformation[16] with a γ-loop formed by a hydrogen bridge between the CH_2NH and the CH_2CO groups and an equatorial alanine methyl group. Chain α is in a stretched C_5 type conformation. A second hydrogen bridge is found between the CH_2NH group of the α chain and the CH_2CO carbonyl of the ß chain. So one carbonyl at the ß-chain forms two bisected hydrogen bonds.

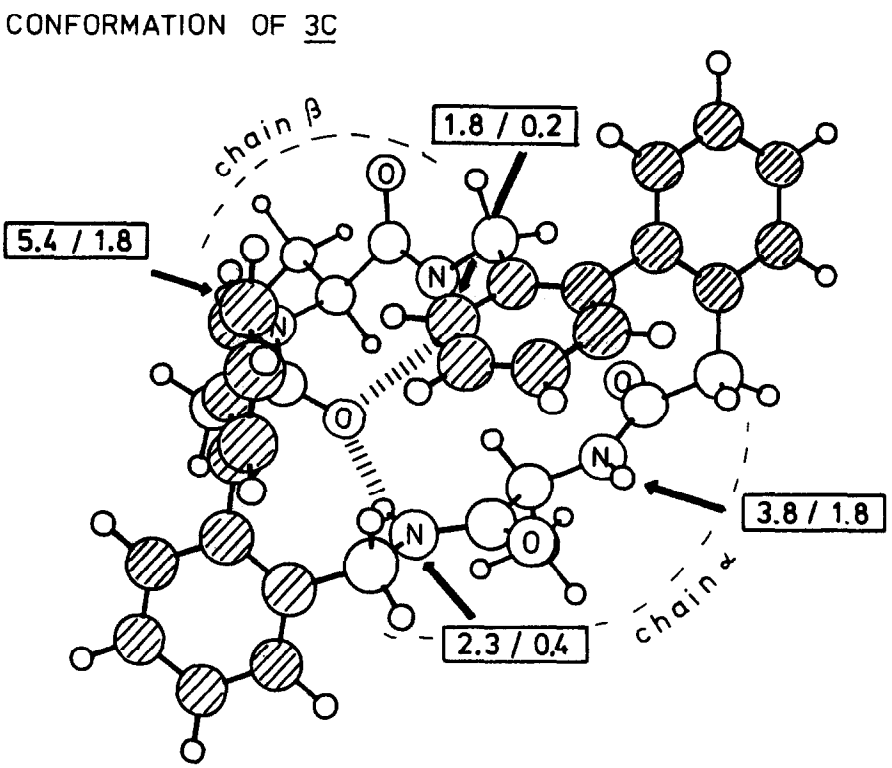


Figure 3: Force field conformation of 3C with perpendicular arrangement of the biphenyl groups. The boxed numbers are the temperature dependence of the NH-protons (10^{-3} ppm/K, left) and the differences of the NH chemical shifts between DMSO and $CDCl_3$ (ppm, right); these data support the indicated hydrogen bonds.

One proton at the ring II of the biphenyl of R-configuration ("b" in Fig. 1) is located directly over the center of ring III of the other biphenyl unit with S-configuration. A conformation similar to that in Fig. 3 but with interchanged biphenyl chirality can also be constructed but the energy is 5.5 kcal/mol higher according to the force field calculations (the methyl groups of the S-alanine links are than directed more inwards to the molecule center, leading to additional steric repulsion).

Coupling constants, NOE connectivities and chemical shifts are in agreement with the geometry of Figure 3: The compilation of dihedral angles derived from the Karplus equation[17] fits reasonably well with the dihedral angles of the conformation in Figure 3 (Tab. 1). Some deviations are found at the CH_2NH groups where the large coupling constants correspond well with the 150 to 160° range given by the MMP2 calculation but the small couplings (2.5 and 1.9 Hz) are still too large to explain the proposed angle of nearly 90°. This can indicate that the form of the Karplus equation derived for peptides is not valid for benzylic CH_2NH groups. However, small torsional deviations (± 20°) will give a better fit.

Table 1: Vicinal Coupling Constants and Derived Dihedral Angles of 3C.

		3J(Hz)	Θ exp	Θ force field
chain α:	αH - NH	6.7	22-32 / 133-145	136
	CH_2 - NH	6.6	24-34 / 130-140	151
		1.9	60-68 / 105-118	-92
chain ß:	αH - NH	8.8	146-158	-146
	CH_2 - NH	9.8	155-175	-156
		2.5	55-63 / 105-115	85

a) Data in $CDCl_3$, values in DMSO are similar (deviation < 1Hz).

The 2D-NOE spectrum of 3C in chloroform (Figure 4) gives a number of connectivities. Each observed cross peak corresponds to a interproton distance less than 3.0 Å found in the MM2 conformation of 3C in Figure 3. Also the reverse statement is true: each calculated MM2 distance less than 3.0 Å gives a NOE cross peak (one exception).

Some problems arise from the intensity of the cross peaks. For example, the geometry in Fig. 3 gives an interchain distance of 2.14 Å between the Ala-αH of the stretched chain α and the CH_2NH of the bent chain (ß). This should result in a very strong NOE but the corresponding cross peak is rather weak. Although MM2 brings the aromatic meta proton (b) of ring II in close contact to one of the CH_2N-protons in chain alpha (2.32 Å), no NMR crosspeak is observed. We think that the conformation of 3 in solution may not be as fixed as it is suggested by Fig. 3. Certainly conformational motions are still present even if the overall arrangement of the biphenyl rings and peptide chains is maintained. Minor movements of the two biphenyl groups will increase the distance mentioned above without changing the basic conformation of 3.

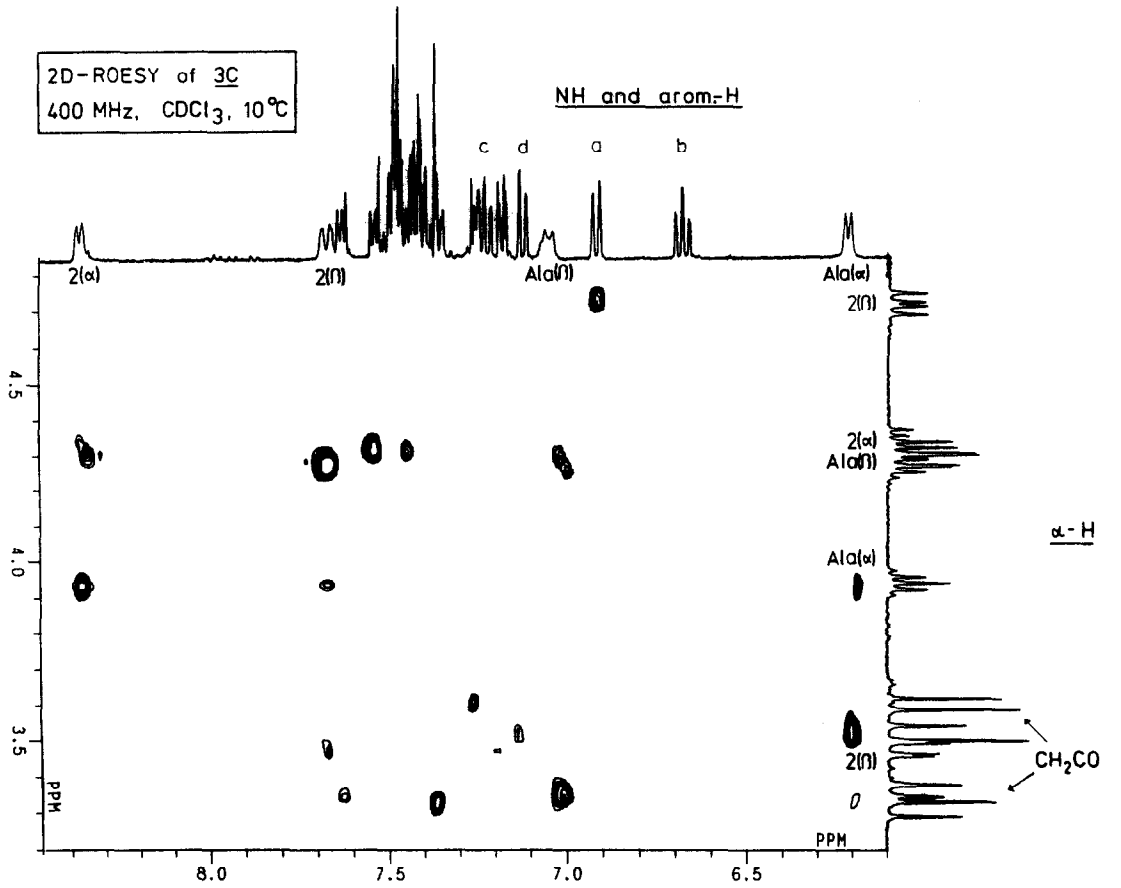


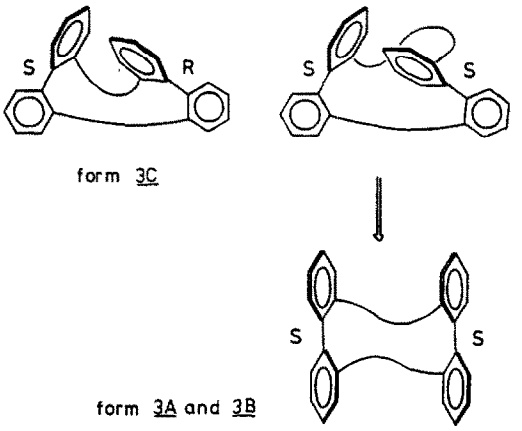
Figure 4: Part of the 400 MHz-2D-ROESY spectrum of 3C in $CDCl_3$ at 10 °C. The spectral parameters are given in the experimental section. The cross peaks between the α-H and the aromatic and NH-region are shown. The assignment of the NH- and αH-protons of the alanine parts and of the two spacers 2 are indicated. The letters in brackets denote the type of the peptide chain (see text and Fig. 3), the aromatic protons (a, b, c and d) are defined in Figure 3. All observed cross peaks correspond to interproton distances less than 3.0Å in the proposed MM2-conformation of 3C (Fig. 3).

Several chemical shifts of 3C are good indicators for the proposed molecular conformation. These include the upfield shift of the protons in ring II sticking into the pi-cloud of ring III as discussed above. In a similar way, the Ala-NH of chain α is located directly over the center of ring II and shifted upfield by 0.6 ppm relative to the Ala-NH of chain ß. The hydrogen bonding of the two CH_2NH protons is supported by two experimental observations: 1. The temperature gradients of the chemical shift of both protons are very low in DMSO[1] 2. Their chemical shifts show only small changes on going from chloroform to DMSO[18] (Fig. 3).

In conclusion all experimental data support the conformation of Figure 3 for the atropisomer 3C.

Conformation of the C_2 forms 3A and 3B

Whereas the R,S configuration of the two biphenyl rings in 3C results in a conformation in which two of the aromatic rings come close together, a similar conformation with R,R or S,S configuration is difficult to construct (Scheme 4).



Scheme 4

The drawing above suggests that 3A or 3B will probably not exist as mixture of fast equilibrating C_1 structures giving apparent C_2 symmetry. Most likely 3A as well as 3B adopt conformations with identical spatial arrangement of the two biphenyl groups (Scheme 4). The conformation within the peptide chains remains to be explored.

The coupling constants and NH-chemical shifts in Table 2 show that 3A and 3B should exist in similar conformations or conformational equilibria. The U-type arrangement of the H-N-CO-C-H fragments is manifested in both geometries by cross peaks in the 2D-NOE spectra. The Ala-NH is trans orientated to the Ala-Hα as indicated by the large coupling constant and the absence of NOE effects between these protons (in 3A and 3B). Other NOE connectivities observed (e.g. between the CH_2-groups and aromatic protons) do not provide additional conformational information. The temperature dependence of the NH-chemical shifts in dimethyl sulfoxide (Table 2) gives no indication of permanent intramolecular hydrogen bonds.

Table 2: Temperature and Solvent Dependence of Chemical Shifts and Vicinal Coupling Constants of Amide Protons in Compound 3A and 3B.

	$\Delta\delta/\Delta T[10^{-3}ppm/K]$(DMSO)		δ DMSO - δ $CDCl_3$		$^3J_{NH\text{-}\alpha H}$ ($CDCl_3$)	
	3A	3B	3A	3B	3A	3B
CH_2NH	4.8	5.8	0.4	0.7	9.4	7.0
					3.0	2.7
AlaNH	3.8	4.7	1.8	1.6	7.5	8.3

The data presented can be explained with a variety of conformations or an equilibrium between them. Two examples are shown in Figure 5. One form contains interchain hydrogen bonds as in a ß-sheet, the other form has in addition two γ-loops. Most likely there is an equilibrium between such forms. In addition, the NH-protons are probably solvated by the solvent dimethyl sulfoxide.

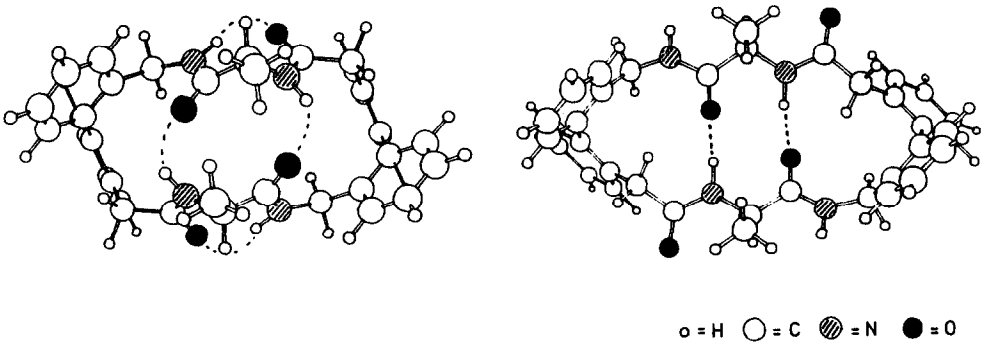


Figure 5: Two conformations (MMP2) of 3A or 3B with different hydrogen bonding. Both forms have C_2 symmetry. The peptide part in the right structure adopts a ß-sheet conformation, the left structure contains two γ-loops.

Conclusions

Naturally, one would expect that the biphenyl configuration in a cyclic molecule like 3 is determined by the chirality (S) of the alanine residues. So one of the three possible diastereomers 3A, 3B or 3C should be favored. However, we find a statistical distribution of the diastereomers in DMSO. Obviously, the intermolecular solvation by DMSO is stronger than the intramolecular interactions (e.g. between NH and CO groups) and the energy differences between 3A, 3B and 3C vanish in DMSO.

In less polar solvents such as chloroform weak intramolecular interactions determine the conformation and one of the isomers (3B) disappears. Unfortunately, we cannot determine the exact conformation of 3A and 3B either in DMSO or chloroform and it is possible that 3A exists as a mixture of equilibrating structures. The detailed reason for the instability of 3B in chloroform is therefore unknown.

The conformation of the form with C_1 symmetry 3C does not change going from chloroform to DMSO. We find an "edge to face" orientation of two benzene rings; the two different peptide chains are in the C_7(eq) and C_5 conformation. The carbonyl oxygen of the C_7 hydrogen bridge is in addition involved in a hydrogen bridge to the opposite peptide chain (see Figure 3). The question is open whether the weak attraction of the edge to face oriented benzene rings[19] is sufficent to stabilize the proposed backbone conformation so even DMSO does not break the hydrogen bonds.

This study does not exclude the proposed function of the bridge 2 as an ß-loop substitute. The C_2 forms 3A and 3B may adopt a ß-sheet conformation, but the C_1 form does not. We plan the synthesis

of similar cyclic compounds with longer peptide chains of known conformational preference[20] to test the ß-loop forming potential of the biphenyl bridge 2. The problems of fast atropisomerism should be avoided using binaphthyl analogues of 2.

EXPERIMENTAL

The NMR spectra were recorded on a JEOL-GX400 instrument (400 MHz for ^1H). The detailed spectral parameters of the 2D-ROESY experiment are: Pulsequency: 90°-(32°-delay)$_X$-FID[23]; 90°-puls = 20 ms, 32°-puls = 7 ms, delay = 70 ms, X = 595 adding up to a total mixing time of 250 ms. Spectral width 3200 Hz. f2 resolution: 1K , f1 resolution: 512 obtained by zero filling of 128 FIDs (128 scans each). Window functions: f2 - none, f1 - trapezoidal.

3,4,5,6 Dibenzooxepinon-2 (5)
22.4g (0.1mol) sublimated anhydride[21] 4 are suspended in 100 ml dry dimethylformamide and cooled to 0 °C. 4.0g (0.1mol) $NaBH_4$ are added within 10 min. After stirring for 1 h at room temper. the mixture is poured into 100 ml 6N HCl and diluted with 300 ml water. The precipitate is filtered off by suction, washed with water, dried and puryfied by sublimation (0.4 torr, 140°C): 19.1 g, 91%; m.p.: 132-134°C. - ^1H-NMR ($CDCl_3$): 8.1-7.4ppm, 12H, arom.; 5.05ppm, 2H, CH_2 (AB). - Anal. ($C_{14}H_{10}O_2$) calc. C, 80.00; H, 4.76; found C, 79.52; H, 4.96%.

2-Phthalimidomethyl-2'-carboxybiphenyl (6)
10.5g (50mmol) 5 and 10.0g (50mmol) potassium phthalimide are refluxed in 100 ml dry dimethylformamide for 15 h. After cooling to room temper. the colourless precipitate is filtered off by suction, suspended in 50 ml acetic acid and stirred for 1 h. 200 ml water are added and the precipitate is filtered off. 12.0g (67%) colourless crystals are obtained by recrystallisation from methanol; m.p.: 197-199°C. - ^1H-NMR:($CDCl_3$) 8.1-7.1 ppm, 8H, arom.; 4.65 ppm, 2H, CH_2 (AB). - Anal. ($C_{22}H_{15}NO_4$) calc. C, 73.95; H, 4.20; N, 3.92; found C, 73.61; H, 4.36; N, 3.86%.

2-Phthalimidomethyl-2'-carboxymethylbiphenyl (7)
10.0g (28mmol) 6, 20ml thionychloride and 50ml dry benzene are stirred under reflux for 1 h. Solvent and excess of thionylchloride are removed under reduced pressure. The residue is taken up with 20 ml dry benzene and evaporated again, leaving an oil which solidifies on treatment with 10 ml petroleum ether (m.p.: 123-125 °C). The petroleum ether is decanted and the acid chloride is dissolved in 100 ml dry dioxane. This solution is added with a dropping funnel to a solution of diazomethane in ether (prepared from 10.0 g N-nitrosomethylurea[22]) at 0 °C and stirred overnight at room temper. After removing ether and the excess of diazomethane the residue is diluted with 200 ml dioxane and 20 ml water. This solution is irradiated with a mercury UV-lamp until nitrogen evolution stopped. The solvent is removed under reduced pressure, the remaining oil is dissolved in 100 ml ethyl acetate and extracted four times with 300 ml saturated $NaHCO_3$ solution. The aqueous solution is acidified with hydrochloric acid and extracted two times with 50 ml methylene chloride. The organic layer is dried over $MgSO_4$. Evaporation gives 5.1 g (49%) 7 as a colourless solid; m.p.: 105 °C decomposition. - ^1H-NMR ($CDCl_3$): 7.8-7.0ppm, 12H, arom.; 4.60ppm, 2H, CH_2N (AB); 3.55ppm, 2H, CH_2CO (AB). - Anal. ($C_{23}H_{17}NO_4$) calc. C, 74.39; H, 4.58; N, 3.77; found C, 73.76; H, 4.92; N 3.97%.

2-Phthalimidomethyl-2'-carboxymethylbiphenyl-AlaOMe (8)
A solution of 2.71 g (7.3 mmol) 7 and 1.01 g (7.3 mmol) H-AlaOMe·HCl in 30 ml dry methylene chloride is cooled to -10 °C and 4.4 ml N-methyl morpholine are added. 5.0 ml propylphosphonic anhydride (50% in CH_2Cl_2) are added by a dropping funnel. The solution is stirred at -10 °C for 1 h and 2 days at room temperature. The solvent is removed under reduced pressure and the residue is taken up in 200 ml ethyl acetate. The solution is washed with saturated $NaHCO_3$ solution, $NaHSO_4$ solution (5%) and brine several times. After drying over $MgSO_4$ the solvent is removed yielding 1.80 g 8 (55%) as an slightly yellow oil which was used without further purification in the next step. - ^1H-NMR ($CDCl_3$, two sets of signals due to biphenyl atropisomerism): 7.9-7.1ppm, 24H, arom.; 6.56ppm, 1H, NH; 6.43ppm, 1H, NH; 4.79-4.50ppm, 6H, CH_2N (2AB) and 2αH; 3.70ppm, 6H, OCH_3; 3.46-3.41ppm, 4H, CH_2CO (2 AB); 1.37-1.35ppm, 6H, CH_3-Ala.

Cyclo(-2-Aminomethyl-2'-carboxymethylbiphenyl-Ala-)$_2$ (3)

1.3 g (2.85mmol) 8 and 2.0ml hydrazine hydrate are stirred in 50ml methanol at 40 °C for 3 h. The solution is evaporated, the excess of hydrazine hydrate removed and the residue treated with 50ml chloroform and filtered. The filtrate is evaporated to dryness, yielding 890mg of 2-AlaNHNH$_2$ 9.

9 is dissolved in 20ml dimethylformamide and cooled to -20 °C. 2.3ml hydrochloric acid and 210mg $NaNO_2$ in 3ml water are added and the solution is stirred for 45 min at -20 °C. 70ml dimethylformamide (cooled to -10 °C) and 4.5ml N-methyl morpholine are added and the solution is allowed to warm up to 5 °C overnight. After stirring at 5 °C for 2 days, the solvent is removed in vacuum (T<50 °C). The residue is dissolved in 200ml ethyl acetate, washed with $NaHCO_3$ solution, water, $NaHSO_4$ solution and brine. After drying over $MgSO_4$ the solution is evaporated to dryness yielding 290mg crude material (36%).

The crude material can be purified by HPLC on silica gel with chloroform/acetone = 4/1 giving 3A and 3C in a 1:2 ratio; treatment of the crude material with a few ml hot acetone gives a colourless precipitate being a 1/1 mixture of 3A and 3B. The total yield of purified material is approximately 20%; m.p.: 3A: 170-172°C; 3C: 182-185°C. ^{1}H-NMR in Figure 1. - Anal. (3·$CHCl_3$:$C_{37}H_{37}N_4O_4Cl_3$) calc. C, 62.80; H, 5.23; N, 7.92; found C, 63.02; H, 5.29; N, 7.71%. - mass spectra: DCI (NH_3, positive), m/z(%)= 589(MH^+,100), 297(3), 277(9). DCI (NH_3, negative) m/z(%) = 587($M-H^-$,100). EI(70 eV) m/z(%) = 588(100), 560(3), 490(7), 278(5), 267(7), 180(8).

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