The determination of the Laue symmetry, crystal class, unit-cell parameters and crystal orientation matrix was by previously described techniques (Churchill, Lashewycz & Rotella, 1977). All data were corrected for Lorentz and polarization effects and placed on an absolute scale. Any reflection with I(net) < 0 was assigned the value $|F_o| = 0$. The systematic extinctions observed were hkl for $h + k = 2n + 1$ and $h0l$ for $l = 2n + 1$; the diffraction symmetry was $2/m$. The two possible monoclinic space groups were Cc [C_s^4; No. 9] and $C2/c$ [C_{2h}^6; No. 15]; the centrosymmetric space group $C2/c$ was determined to be the correct choice.

The structure was solved *via* an automatic Patterson routine (*SHELXTL-Plus*88; Sheldrick, 1988) and refined by full-matrix least-squares techniques. The molecule is located about a twofold rotation axis (1/2, y, 1/4). H atoms were located from a difference Fourier synthesis and refined with isotropic temperature factors. All crystallographic calculations were performed using either the UCI-modified version of the *UCLA Crystallographic Computing Package* (Strouse, 1981) or *SHELXTL-Plus*. Molecular graphics were drawn with *ORTEP*II (Johnson, 1976).

Acknowledgement is made to the National Science Foundation for support of this research (CHE-90-15849) and for the purchase of the Siemens $R3m/V$ diffractometer system (CHE-85-14495).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: HH1027). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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[Aib^{5,6}-D-Ala^8]-Cyclolinopeptide A, Grown from a Benzene/Acetonitrile Mixture

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(*Received* 7 *February* 1994; *accepted* 13 *June* 1994)

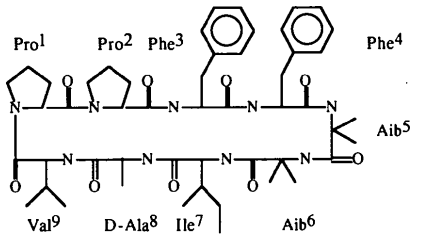
Abstract

cyclo-(Prolyl-prolyl-phenylalanyl-phenylalanyl-α-aminoisobutyryl-α-aminoisobutyryl-isoleucyl-D-alanyl-valyl) ([Aib^{5,6}-D-Ala^8]-cyclolinopeptide A), grown from benzene/acetonitrile mixture, crystallizes with one acetonitrile and two water molecules. The molecular structure is almost identical to that obtained from methanol/water. The dimension of the solvent channels found in these structures is reduced in the present one, but the intramolecular hydrogen-bond pattern is preserved. The Pro^1-Pro^2 peptide unit is *cis* ($\omega = 8°$); all others are *trans*.

Comment

Cyclolinopeptide A (CLA), a homodetic nonapeptide of sequence *cyclo*-(Pro^1-Pro^2-Phe^3-Phe^4-Leu^5-Ile^6-Ile^7-Leu^8-Val^9), isolated from linseed (Kaufmann & Tobshirbel, 1959), belongs to a class of cyclic peptides well known for their competitive inhibitory activity towards the cholate uptake in hepatocytes (Kessler, Klein, Müller, Wagner, Bats, Ziegler & Frimmer, 1986; Di Blasio, Rossi, Benedetti, Pavone, Pedone, Temussi, Zanotti & Tancredi, 1989). Various synthetic analogues were synthetized and characterized in our laboratories (Zanotti, Tancredi, Rossi, Benedetti, Pedone & Temussi, 1989; Di Blasio, Rossi, Benedetti, Pavone, Saviano, Pedone, Zanotti & Tancredi, 1992; Zanotti, Maione, Rossi, Saviano, Pedone & Tancredi, 1993; Rossi, Saviano, Di Blasio, Zanotti, Maione, Tancredi & Pedone, 1994) in order to investigate the structure–activity relationships of CLA. Recently, the conformational analysis of one of these analogues, [Aib^{5,6}-D-Ala^8]-cyclolinopeptide A (CLAIB) grown from a methanol/water mixture,

has been reported (Di Blasio, Rossi, Benedetti, Pavone, Saviano, Pedone, Zanotti & Tancredi, 1992).



CLAIB

As part of a systematic investigation of the influence of solvents with different polarity on conformation and packing in the crystals of bioactive molecules, we report here the X-ray analysis of [Aib^{5,6}-D-Ala^8]-cyclolinopeptide A grown from a benzene/acetonitrile mixture.

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	B_{eq}
N1	0.1449 (1)	0.3088 (2)	0.7989 (5)	3.53 (8)
C$^\alpha$1	0.1658 (2)	0.3619 (3)	0.7220 (7)	3.89 (8)
C$^\beta$1	0.1448 (2)	0.4273 (4)	0.7809 (9)	5.29 (9)
C$^\gamma$1	0.1289 (4)	0.4065 (5)	0.9198 (11)	8.71 (9)
C$^\delta$1	0.1172 (2)	0.3349 (4)	0.9105 (8)	5.07 (9)
C′1	0.2175 (2)	0.3616 (3)	0.7450 (7)	3.90 (8)
O1	0.2337 (1)	0.3342 (2)	0.8429 (5)	5.12 (8)
N2	0.2421 (2)	0.3952 (3)	0.6528 (6)	4.01 (8)
C$^\alpha$2	0.2256 (2)	0.4382 (3)	0.5431 (7)	4.26 (8)
C$^\beta$2	0.2634 (3)	0.4901 (4)	0.5290 (9)	6.08 (9)
C$^\gamma$2	0.3047 (2)	0.4507 (4)	0.5628 (8)	5.69 (9)
C$^\delta$2	0.2910 (2)	0.4051 (4)	0.6791 (9)	5.29 (9)
C′2	0.2164 (2)	0.4019 (3)	0.4111 (7)	4.15 (8)
O2	0.1939 (2)	0.4318 (3)	0.3261 (6)	6.92 (8)
N3	0.2329 (2)	0.3415 (3)	0.3910 (5)	3.85 (8)
C$^\alpha$3	0.2276 (2)	0.3081 (3)	0.2621 (6)	4.17 (8)
C$^\beta$3	0.2704 (2)	0.2693 (4)	0.2205 (8)	5.22 (9)
C$^\gamma$3	0.3100 (2)	0.3155 (4)	0.2002 (7)	4.32 (8)
C$^{\delta1}$3	0.3440 (3)	0.3187 (5)	0.2978 (8)	5.96 (9)
C$^{\delta2}$3	0.3137 (2)	0.3551 (4)	0.0867 (8)	5.20 (9)
C$^{\varepsilon1}$3	0.3804 (3)	0.3634 (5)	0.2794 (10)	7.13 (9)
C$^{\varepsilon2}$3	0.3505 (3)	0.3978 (4)	0.0698 (9)	6.02 (9)
C3ζ	0.3839 (3)	0.4003 (4)	0.1673 (10)	6.62 (9)
C′3	0.1881 (2)	0.2591 (3)	0.2571 (7)	4.28 (8)
O3	0.1645 (2)	0.2550 (3)	0.1562 (5)	6.15 (8)
N4	0.1809 (2)	0.2214 (3)	0.3677 (5)	3.72 (8)
C$^\alpha$4	0.1485 (2)	0.1662 (3)	0.3668 (6)	3.66 (8)
C$^\beta$4	0.1667 (2)	0.1054 (4)	0.4398 (7)	4.65 (8)
C$^\gamma$4	0.2024 (3)	0.0702 (4)	0.3586 (7)	4.98 (9)
C$^{\delta1}$4	0.2465 (3)	0.0920 (4)	0.3616 (9)	6.14 (9)
C$^{\delta2}$4	0.1912 (3)	0.0175 (4)	0.2720 (9)	6.80 (9)
C$^{\varepsilon1}$4	0.2794 (3)	0.0629 (5)	0.2771 (11)	7.99 (9)
C$^{\varepsilon2}$4	0.2244 (4)	−0.0123 (5)	0.1875 (10)	7.92 (9)
C4ζ	0.2656 (4)	0.0129 (6)	0.1948 (10)	8.56 (9)
C′4	0.1026 (2)	0.1900 (3)	0.4185 (6)	3.83 (8)
O4	0.0828 (1)	0.1623 (2)	0.5128 (4)	4.03 (7)
N5	0.0854 (2)	0.2407 (3)	0.3483 (6)	4.39 (8)
C$^\alpha$5	0.0425 (2)	0.2726 (3)	0.3824 (7)	4.51 (8)
C$^{\beta1}$5	0.0478 (3)	0.3120 (4)	0.5140 (8)	6.02 (9)
C$^{\beta2}$5	0.0291 (3)	0.3211 (4)	0.2668 (9)	6.25 (9)
C′5	0.0054 (2)	0.2189 (4)	0.3928 (7)	4.43 (8)
O5	−0.0231 (1)	0.2209 (3)	0.4837 (5)	5.35 (7)
N6	0.0060 (2)	0.1715 (3)	0.2971 (5)	4.41 (8)
C$^\alpha$6	−0.0286 (2)	0.1196 (4)	0.2799 (7)	5.42 (8)
C$^{\beta1}$6	−0.0108 (3)	0.0674 (5)	0.1770 (8)	7.17 (9)
C$^{\beta2}$6	−0.0706 (3)	0.1511 (6)	0.2290 (10)	8.44 (9)
C′6	−0.0369 (2)	0.0802 (4)	0.4108 (7)	4.59 (8)
O6	−0.0729 (1)	0.0520 (3)	0.4306 (5)	6.15 (8)
N7	−0.0016 (2)	0.0714 (3)	0.4910 (5)	3.83 (8)
C$^\alpha$7	−0.0038 (2)	0.0297 (3)	0.6098 (6)	4.11 (8)
C$^\beta$7	0.0256 (3)	−0.0336 (4)	0.5985 (7)	5.20 (9)
C$^{\gamma1}$7	0.0739 (3)	−0.0161 (4)	0.5803 (9)	6.60 (9)
C$^{\gamma2}$7	0.0082 (3)	−0.0772 (4)	0.4835 (9)	6.42 (9)
C$^\delta$7	0.1059 (4)	−0.0767 (7)	0.5903 (14)	11.90 (9)
C′7	0.0045 (2)	0.0701 (4)	0.7383 (6)	4.27 (8)
O7	0.0130 (2)	0.0410 (3)	0.8453 (5)	6.18 (8)
N8	0.0013 (2)	0.1374 (3)	0.7307 (5)	3.84 (8)
C$^\alpha$8	0.0030 (2)	0.1776 (4)	0.8551 (6)	4.36 (8)
C$^\beta$8	−0.0175 (3)	0.2453 (5)	0.8342 (8)	6.45 (9)
C′8	0.0511 (2)	0.1856 (3)	0.9106 (6)	4.17 (8)
O8	0.0559 (1)	0.1977 (3)	1.0309 (4)	5.47 (7)
N9	0.0849 (2)	0.1827 (3)	0.8214 (5)	3.72 (8)
C$^\alpha$9	0.1318 (2)	0.1906 (3)	0.8609 (6)	3.70 (8)
C$^\beta$9	0.1576 (2)	0.1244 (3)	0.8583 (7)	4.52 (8)
C$^{\gamma1}$9	0.1338 (3)	0.0709 (4)	0.9399 (8)	5.99 (9)
C$^{\gamma2}$9	0.2047 (3)	0.1348 (4)	0.9140 (9)	6.59 (9)
C′9	0.1523 (2)	0.2439 (3)	0.7698 (6)	3.39 (8)
O9	0.1753 (1)	0.2289 (2)	0.6694 (4)	4.31 (7)
O1*w*	−0.1038 (3)	−0.0373 (5)	0.2096 (10)	13.40 (9)
O2*w*	0.0853 (5)	−0.1128 (9)	0.0163 (16)	28.05 (9)
N1*s*	0.2325 (3)	−0.2352 (4)	0.0743 (7)	7.42 (9)
C1*s*	0.1988 (5)	−0.2207 (9)	0.1669 (14)	16.93 (9)
C2*s*	0.1783 (6)	−0.2027 (9)	0.3164 (15)	18.13 (9)

A stereo drawing of the molecular structure of the cyclic nonapeptide CLAIB, with intramolecular hydrogen bonds, is shown in Fig. 1. The geometric parameters of all residues in the CLAIB structure are unexceptional. The average bond distances and bond angles, involving both the backbone and side-chain atoms, compare well with literature values for other peptides of a similar size (Benedetti, 1982; Benedetti, Morelli, Nemethy & Scheraga, 1983). The conformational parameters of the backbone and of the side chains are listed in Table 2.

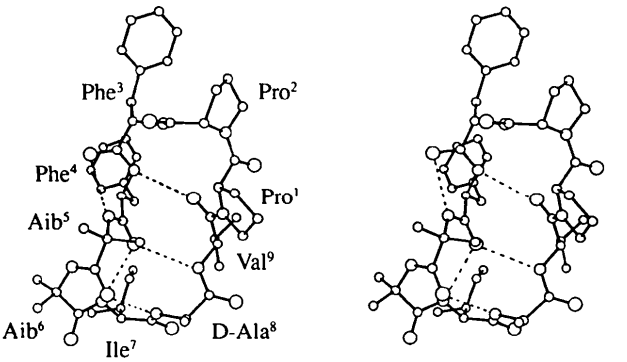


Fig. 1. Stereo drawing of the CLAIB molecule, with the residue labelling. The intramolecular hydrogen bonds are represented as dashed lines.

As in the previous crystal structure of CLAIB (grown from methanol/water), the Pro^1—Pro^2 peptide bond is *cis* ($\omega = 8°$); all the other are *trans*. The overall solid-state CLAIB structure is very similar to

Table 2. *Conformational parameters for CLAIB*

	Pro[1]	Pro[2]	Phe[3]	Phe[4]	Aib[5]	Aib[6]	Ile[7]	D-Ala[8]	Val[9]
φ_i (N_i—C^{α}_i)*	−67	−90	−96	−94	−54	−53	−117	77	−129
ψ_i (C^{α}_i—C'_i)	162	−16	−40	58	−42	−33	17	27	80
ω_i (C'_i—N_{i+1})	8	−175	−171	−178	−174	−174	172	179	176
$\chi^{1,1}_i$	22	33	−63	−73			−63		−174
$\chi^{1,2}_i$							61		−53
$\chi^{2,1}_i$			−76	84			171		
$\chi^{2,2}_i$			104	−92					

* Standard deviations for the individual torsion angles around bonds of the peptide backbone and around bonds of the amino acid side chains are approximately 0.5 and 1.1°, respectively.

that found for crystals of CLAIB grown from methanol/water mixture, with the same intramolecular hydrogen-bond pattern. The root-mean-square deviation when the backbones of the two structures are superimposed is 0.18 Å and the maximum variation of the torsion angles is 3°.

The hydrogen-bond details for CLAIB are shown in Table 3. The 27-membered ring is conformationally stabilized by five transannular hydrogen bonds, one of the 1←5 type (α-turn), two of the 1←4 type (β-turns), one of the 1←3 type (γ-turn), and a C17 structure (Benedetti, 1982).

Fig. 2 shows the packing mode of the CLAIB molecules as viewed along the *c* axis. The peptide molecules in the crystal are held together by a network of intermolecular hydrogen bonds involving the two hydrogen-bond donor groups N3-H and N6-H, which are not involved in the intramolecular hydrogen-bond scheme, and the three solvent molecules. Each peptide molecule packs one on the top of the other *via* one intramolecular N—H···O=C′ hydrogen bond [N6—H···O8=C′8 3.07 (1) Å] which involves molecules translated along the *c* axis. Long rows of hydrogen-bonded peptide molecules are thus formed. The intermolecular hydrogen bonds between these peptide rows involve an acetonitrile and a water (O2*w*) molecule and produce a layer of rows and solvent molecules parallel to the *ac* plane. Perpendicular to this plane, the layers pack together *via* the O1*w* molecule, which acts as a bridge by the formation of intermolecular hydrogen bonds with cyclic molecules of adjacent layers. Along the **b** direction, van der Waals interactions between hydrophobic groups further stabilize the layers. Along the *c* axis, the solvent molecules are aligned one on top of the other to form part of a channel, similar to those observed in other cyclic peptide structures (Karle & Duesler, 1977).

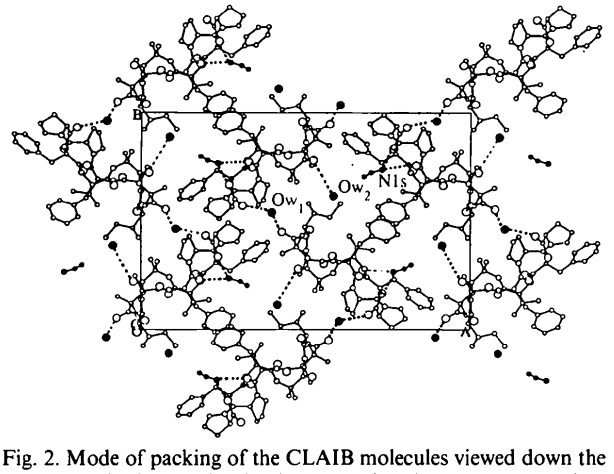


Fig. 2. Mode of packing of the CLAIB molecules viewed down the *c* axis. The intermolecular hydrogen bonds are represented as dashed lines.

In conclusion, the presence of different solvents does not alter the conformation of the peptide. The only result of using benzene/acetonitrile solvent is the formation of reduced volume channels, accommodating only one acetonitrile and two water molecules, compared with CLAIB from methanol/water, which has two water and two methanol molecules.

Experimental

Crystal data

$C_{50}H_{71}N_9O_9.C_2H_3N.2H_2O$
M_r = 1019.2
Orthorhombic
$P2_12_12_1$
a = 29.835 (5) Å
b = 19.784 (2) Å
c = 9.913 (1) Å
V = 5851 (1) Å^3
Z = 4
D_x = 1.157 Mg m^{-3}

Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 25 reflections
θ = 20–24°
μ = 0.573 mm^{-1}
T = 293 K
Needle
0.5 × 0.4 × 0.2 mm
Colourless
Crystal source: slow evaporation from benzene/acetonitrile

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
5786 measured reflections
5754 independent reflections
4162 observed reflections [$I \geq 3.0\sigma(I)$]

θ_{max} = 70°
h = 0 → 36
k = 0 → 24
l = 0 → 12
2 standard reflections
frequency: 60 min
intensity decay: 3%

Refinement

Refinement on F
R = 0.068
wR = 0.071

$(\Delta/\sigma)_{max}$ = 0.19
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

$S = 2.18$
4162 reflections
658 parameters
H-atom parameters not refined
$w = 1/\sigma^2(F_o)$

Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 3. *Hydrogen bonds* (Å, °)

Type*	*D*—H	*A*	*D*···*A*	N···O=C′
Intramolecular				
C7	N5	O3	3.045 (8)	86 (1)
C10	N7	O4	3.102 (7)	126 (1)
C10	N8	O5	3.042 (7)	114 (1)
C13	N4	O9	2.998 (6)	147 (1)
C17	N9	O4	3.086 (6)	133 (1)
Intermolecular	N6	$O8^{i}$	3.07 (1)	120 (1)
Peptide solvent	N3	$N1s^{ii}$	2.96 (4)	
	N1*s*	$O9^{ii}$	2.91 (3)	140 (2)
	O1*w*	O6	2.96 (1)	115 (1)
	O1*w*	$O2^{iii}$	2.78 (5)	136 (3)
	O2*w*	$O5^{iii}$	3.78 (4)	111 (1)

Symmetry codes: (i) $x, y, 1-z$; (ii) $\frac{1}{2}-x, -y, \frac{1}{2}+z$; (iii) $-x, \frac{1}{2}+y, \frac{1}{2}-z$.

* Benedetti (1982).

Direct application of the phase determination procedures failed to give sensible interpretations of the *E* map. The phase problem of CLAIB was overcome by applying the molecular replacement technique using a molecular fragment of known structure. In fact, the coordinates of the Pro-Pro-Phe-Phe fragment, as determined previously in the structure of CLAIB grown from methanol/water, were used as a starting model for the vector search procedure on the set of diffraction data collected with the Patterson search program *PATSEE* (Egert, 1983). The initial model, containing 34 atoms, was correctly orientated and positioned with respect to the origin of the new unit cell. Then the best solution of this procedure was used in the *SIR*92 (Altomare, Cascarano, Giacovazzo, Guagliardi, Polidori, Burla & Camalli, 1994) program with the *PARTIAL* procedure. The direct phase-expansion procedure led to a molecular fragment containing all non-H atoms. Subsequent difference Fourier analysis revealed the two water and acetonitrile molecules. The H atoms were introduced in their stereochemically expected positions with an isotropic temperature factor equal to the B_{eq} of the heavy atom to which they are bonded. Their parameters were kept fixed. The structure was refined using *SHELX*76 (Sheldrick, 1976) on a MicroVAX 3100 computer.

This work was supported by CNR grant No. 89.05354.M277.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1092). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1995). C**51**, 666-670

Two Steroidal Epimers, (5β,17α)-Pregna-20-yno[3,4-*c*][1,2,5]oxadiazol-17-ol (the 5β-Epimer) and (5α,17α)-Pregna-20-yno[3,4-*c*][1,2,5]oxadiazol-17-ol (the 5α-Epimer)

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(*Received* 8 *November* 1993; *accepted* 23 *June* 1994)

Abstract

The crystal and molecular structures of the steroidal oxadiazoles (5β,17α)-pregna-20-yno[3,4-*c*][1,2,5]oxadiazol-17-ol (the 5β-epimer) and (5α,17α)-pregna-20-yno[3,4-*c*][1,2,5]oxadiazol-17-ol (the 5α-epimer), $C_{21}H_{28}N_2O_2$, have been determined. In both structures rings *A* are similar, having conformations intermediate between a strained sofa, a half-chair and an envelope. Rings *B* and *C* are also similar, adopting