**Experimental.** Crystals were grown by controlled diffusion of ethyl acetate into saturated methanol solution. $D_m$ by flotation in $CCl_4$/hexane. Space group and cell parameters determined by rotation and Weissenberg methods; cell dimensions refined by least squares using 25 high-angle reflections on a Nonius CAD-4 diffractometer. Intensity data collected on the diffractometer with $\omega$–$2\theta$ scans using graphite-monochromated Cu $K\alpha$ radiation. Crystal 0·05 x 0·08 x 1.43 mm. $\theta_{max} = 60°$. Two standard reflections (103 and $11\bar{2}$) monitored at regular intervals, crystal stable to X-rays. Intensities not corrected for absorption ($\mu r \simeq 0{\cdot}05$). Out of 915 unique reflections measured up to $\theta = 60°$, 820 considered significant [$|F| \geq 2\sigma(|F|)$]. Index range h $\pm$ 10, k 0/6, $l$ 0/12. Structure solved using *MULTAN*80 (Germain, Main & Woolfson, **1971; P.** Main, **1980,** private communication). The $E$ map calculated with the phases corresponding to the best set revealed six atoms of the diketopiperazine ring. Karle recycling (Karle, **1968)** with these atoms gave the other 11 nonhydrogen atoms. Full-matrix least-squares refinement on $F$ (*SHELX*76, Sheldrick, **1976)** with positional and isotropic temperature factors of non-H atoms converged at $R = 0{\cdot}13$; inclusion of anisotropic temperature factors reduced $R$ to 0·087. At this stage all the H atoms could be located from a difference map. $R$ reduced to 0·065 when the refinement was carried out with inclusion of the H atoms in the structure factor calculation and with an individual weight, $w \propto 1/\sigma^2(|F|)$. H-atom positions were not refined. All H atoms were given an isotropic temperature factor ($U$) of 0.050 Å$^2$. In the final cycle of refinement, $\Delta/\sigma < 0{\cdot}1$ and $wR = 0.071$. $Ap$ in final difference map within +0·3 and –0·3 e Å$^{-3}$.

**Discussion.** Final parameters are listed in Table 1.* Fig. 1 shows the *cyclo*(-α-aminoisobutyryl-L-phenylalanyl-) molecule with the numbering scheme.

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, bond distances and angles involving H atoms, torsion angles and Tables 3, 4 and 5 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39813 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

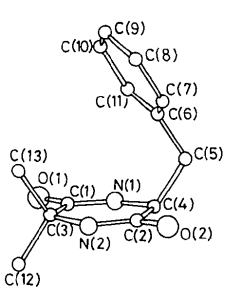


Fig. 1. View of the molecule showing the folded geometry of the phenylalanyl residue.

Table 2 lists the bond lengths, bond angles and selected torsion angles (IUPAC–IUB Commission on Biochemical Nomenclature, **1970)** involving the non-hydrogen atoms, and also the hydrogen-bonding parameters involving the non-hydrogen atoms. The torsion angles $\omega_1$, $\omega_2$ [−1·5 (9), −4·2 (10)°, Table 2] about the peptide bond show that the peptide units are nearly planar. Thus the peptide conformation compares more favourably with that of *cyclo*(-Gly-L-Trp-) ($\omega_1$, $\omega_2 = 3, -3°$) (Morris, Geddes & Sheldrick, **1974)** than

Table 1. Fractional coordinates (x $10^4$) and equivalent isotropic temperature *factors* of *non*-H atoms with *e.s.d.'s* in parentheses

$$U_{eq} = \tfrac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

| | x | y | z | $U_{eq}$(Å$^2$) |
|---|---|---|---|---|
| O(1) | 7024 (5) | −4452 | 92 10 (4) | 0·053 (3) |
| O(2) | 9840 (5) | 2712 (8) | 8266 (4) | 0.044 (3) |
| N(1) | 8944 (6) | −2932 (9) | 8658 (4) | 0·033 (3) |
| N(2) | 7979 (6) | 1212 (9) | 8859 (5) | 0.037 (3) |
| C(1) | 7693 (7) | −2807 (10) | 8978 (6) | 0·034 (4) |
| C(2) | 9193 (7) | 1094 (11) | 8499 (5) | 0.030 (3) |
| C(3) | 7026 (7) | −554 (11) | 9076 (6) | 0.036 (4) |
| C(4) | 9813 (6) | −1144 (10) | 8342 (5) | 0.028 (3) |
| C(5) | 10078 (7) | −1417 (11) | 6995 (6) | 0.042 (4) |
| C(6) | 8765 (6) | −1273 (11) | 5972 (5) | 0·039 (4) |
| C(7) | 8408 (8) | 704 (12) | 5346 (6) | 0.055 (4) |
| C(8) | 7201 (9) | 851 (16) | 4417 (6) | 0.065 (5) |
| C(9) | 6279 (9) | −900 (18) | 4111 (6) | 0.074 (5) |
| C(10) | 6622 (10) | −2824 (15) | 4752 (8) | 0.075 (6) |
| C(11) | 7866 (9) | −3032 (12) | 5652 (6) | 0·057 (4) |
| C(12) | 6753 (7) | −296 (11) | 10431 (6) | 0·050 (4) |
| C(13) | 5645 (7) | −463 (12) | 81 10 (6) | 0.050 (4) |

Table 2. Bond distances (Å), bond angles (°), selected torsion angles (°) and hydrogen-bond geometry

| | | | |
|---|---|---|---|
| C(1)–O(1) | 1.250 (7) | C(2)–N(2) | 1.309 (9) |
| C(1)–N(1) | 1.324 (9) | C(4)–C(5) | 1.532 (8) |
| C(1)–C(3) | 1·537 (9) | C(5)–C(6) | 1.498 (9) |
| N(1)–C(4) | 1.463 (8) | C(6)–C(7) | 1.395 (10) |
| C(3)–C(12) | 1.542 (9) | C(7)–C(8) | 1.371 (10) |
| C(3)–C(13) | 1.511 (9) | C(8)–C(9) | 1.390 (14) |
| C(3)–N(2) | 1·470 (9) | C(9)–C(10) | 1.372 (14) |
| C(2)–C(4) | 1.521 (9) | C(10)–C(11) | 1.382 (12) |
| C(2)–O(2) | 1·226 (8) | C(6)–C(11) | 1.382 (10) |

| | | | |
|---|---|---|---|
| N(1)–C(1)–O(1) | 122.8 (6) | C(4)–C(2)–O(2) | 118·7 (6) |
| N(1)–C(1)–C(3) | 119.1 (6) | N(1)–C(4)–C(2) | 113.2 (5) |
| O(1)–C(1)–C(3) | 118.1 (6) | N(1)–C(4)–C(5) | 110.7 (5) |
| C(12)–C(3)–C(13) | 110·3 (5) | C(2)–C(4)–C(5) | 110·5 (5) |
| C(1)–C(3)–C(12) | 108.2 (5) | C(4)–C(5)–C(6) | 114·0 (5) |
| C(1)–C(3)–N(2) | 111·5 (5) | C(5)–C(6)–C(7) | 119.5 (6) |
| N(2)–C(3)–C(13) | 110.8 (5) | C(5)–C(6)–C(11) | 121.9 (6) |
| N(2)–C(3)–C(12) | 108.0 (5) | C(7)–C(6)–C(11) | 118·6 (6) |
| C(1)–C(3)–C(13) | 107.9 (5) | C(6)–C(11)–C(10) | 120.7 (7) |
| C(1)–N(1)–C(4) | 127.9 (5) | C(11)–C(10)–C(9) | 121.0 (8) |
| C(2)–N(2)–C(3) | 129.3 (5) | C(10)–C(9)–C(8) | 118.0 (8) |
| N(2)–C(2)–C(4) | 118·6 (6) | C(9)–C(8)–C(7) | 121.8 (8) |
| N(2)–C(2)–O(2) | 122.7 (6) | C(8)–C(7)–C(6) | 119.7 (7) |

| | | | |
|---|---|---|---|
| C(3)–C(1)–N(1)–C(4) | −1.5 (9) | C(1)–N(1)–C(4)–C(5) | −120.5 (7) |
| C(1)–N(1)–C(4)–C(2) | 4.2 (9) | N(2)–C(2)–C(4)–C(5) | 123.4 (6) |
| N(1)–C(4)–C(2)–N(2) | −1.4 (8) | N(1)–C(4)–C(5)–C(6) | 64.6 (7) |
| C(4)–C(2)–N(2)–C(3) | −4.2 (10) | C(2)–C(4)–C(5)–C(6) | −61.7 (7) |
| C(2)–N(2)–C(3)–C(1) | 6.7 (9) | C(4)–C(5)–C(6)–C(11) | −81.6 (8) |
| N(2)–C(3)–C(1)–N(1) | −3.6 (8) | C(4)–C(5)–C(6)–C(7) | 96.4 (7) |

Hydrogen-bonding geometry

| | N···O |
|---|---|
| N(1)–H(1)···O(2$^{i}$) | 2.866 (6) Å |
| N(2)–H(2)···O(1$^{ii}$) | 2.865 (7) |

Symmetry code: (i) $x$, 1 − $y$, $z$; (ii) $x$, 1 + $y$, $z$.

with that of *cyclo*(-Gly-L-Tyr-) ($\omega_1, \omega_2 = -4, -7°$) (Lin & Webb, 1973). The torsion angles $\varphi$, $\psi$ and $\omega$ of the peptide backbone [$\varphi_{Aib} = 6{\cdot}7$ (9), $\psi_{Aib} = -3{\cdot}6$ (8), $\omega_{Aib} = -1{\cdot}5$ (9), $\varphi_{Phe} = 4{\cdot}2$ (9), $\psi_{Phe} = -1{\cdot}4$ (8), $\omega_{Phe} = -4.2$ (10)°] (Table 2) indicate that the diketopiperazine ring assumes a flat boat conformation.

The bond lengths (Table 3, deposited) and bond angles (Table 4, deposited) of the Aib residue compare well with those found in *cyclo*(-Aib-Aib-) and *cyclo*(-Aib-L-isoleucyl-) (Suguna ***et al.,*** 1982). The bond angle $C^{\alpha}-N-C'$ ($\tau_n$) in these three compounds [129·3 (6), 130·1 (3) and 127·9 (7)°], however, is significantly greater than the average value (122·1°) found in Aib-containing linear peptides (Paterson, Rumsey, Benedetti, Nemethy & Scheraga 1981). This feature is observed in many cyclic dipeptides, ***e.g.*** *cyclo*(-Gly-Gly-) (126·0°) (Degeilh & Marsh, 1959), *cyclo*(-D-Ala-L-Ala-) (127·9°) (Sletten, 1970), *cyclo*(-L-Ala-L-Ala-) (126.2, 125.2") (Sletten, 1970), *cyclo*(-Gly-L-Tyr-) (126·0, 126·9°) (Lin & Webb, 1973) and *cyclo*(-L-Ser-L-Tyr-) (128.3, 127·4°) (Lin & Webb, 1973).

The molecule is in a folded conformation as shown in Fig. 1. The phenylalanyl $C^{\alpha}$ atom occupies an axial position with $\chi^1 = N(1)-C(4)-C(5)-C(6) = 64{\cdot}6$ (7) and $\chi^2 = C(4)-C(5)-C(6)-C(7) = 96{\cdot}4$ (7)°. These values are in good agreement with those corresponding to the theoretically calculated minimum-energy conformation for the Phe residue ($\chi^1 = 60, \chi^2 = 90°$) (Caillet, Pullman & Maigret, 1971; Chandrasekaran, Lakshminarayanan, Mohanakrishnan & Ramachandran, 1973).

The folded conformation for the molecule is consistent with the situation observed in other diketopiperazines containing the phenylalanyl and tyrosyl residues (Table **5,** deposited), such as *cyclo*(-L-Pro-L-Phe-) (Ramani, Venkatesan, Marsh & Hu Kung, 1976), *cyclo*(-*N*-Me-L-Phe-*N*-Me-D-Phe-) (Benedetti, Marsh & Goodman 1976), *cyclo*(-Gly-L-Tyr-) (Lin & Webb, 1973) and *cyclo*(-L-Ser-L-Tyr-) monohydrate (Lin & Webb, 1973). However, in the case of *cyclo*(-*N*-Me-L-$Phe_2$-) (Benedetti ***et al.,*** 1976) one of the phenylalanyl rings folds over the diketopiperazine ring whereas the other is forced away from this ring to avoid steric repulsions.

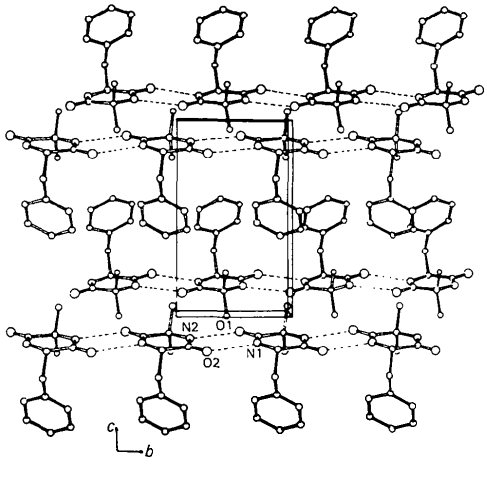


**Fig. 2. Packing of the molecules viewed down the *a** axis.**

In the solid-state conformation, one of the Aib CH, groups is located close to the phenyl ring [C(13) is 4·07 Å from the midpoint of the benzene ring]. The 100 MHz $^1H$ NMR spectrum of *cyclo*(-Aib-L-Phe-) in trifluoroacetic acid solution reveals a large chemical shift difference of 0·69 p.p.m. between the two Aib CH, groups. The abnormally high field resonance at 0·88 p.p.m. (from tetramethylsilane reference) is due to the CH, group proximal to the benzene ring. This suggests that the folding pattern of the Phe side chain observed in the crystal structure is maintained in solution.

The crystal structure is stabilized by N–H···O hydrogen bonds (Fig. 2). Each molecule forms a pair of hydrogen bonds to adjacent b-translated molecules (Table 2). The hydrophobic and hydrophilic groups are neatly segregated into adjacent layers parallel to the c axis.

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