Structure of an N-Monomethylated Cyclic Dipeptide, cyclo(-N-Methyl-L-phenylalanyl-L-phenylalanyl-)

BY MARIA GDANIEC

Faculty of Chemistry, A. Mickiewicz University, Grunwaldzka 6, 60-780 Poznán, Poland

AND BOGDAN LIBEREK

Institute of Chemistry, University of Gdańsk, 80-952 Gdańsk, Poland

(Received 23 June 1986; accepted 22 December 1986)

Abstract. 1-Methyl-3,6-bis(phenylmethyl)-2,5-piperazinedione, C\textsubscript{19}H\textsubscript{20}N\textsubscript{2}O\textsubscript{2}, M\textsubscript{r}=308.3, orthorhombic, P\textsubscript{2}\textsubscript{1}2\textsubscript{1}2\textsubscript{1}, a = 10.254 (2), b = 13.370 (3), c = 24.294 (4) Å, V = 3330 (1) Å\textsuperscript{3}, \(Z = 8\), \(D\textsubscript{x} = 1.23\) g cm\textsuperscript{-3}, \(\lambda(Cu\textsubscript{K\alpha}) = 1.54178\) Å, \(\mu = 5.6\) cm\textsuperscript{-1}, \(F(000) = 1312\), room temperature, \(R = 0.052\) for 1697 observed reflections. Two crystallographically independent molecules joined through a pair of N-H...O hydrogen bonds form dimers as distinct units in the crystal lattice. The general molecular conformation is similar to that of cyclo(L-Phe)\textsubscript{2} (Gdaniec & Liberek, 1986). In molecule B, the aromatic side chain of the N-methylated phenylalanine residue folds over the diketopiperazine moiety \([\chi_1 = 61.1 (7)^\circ]\) while the other side chain is in extended conformation \([\chi_2 = -62.5 (6)^\circ]\). The opposite conformation of the side chains is observed in molecule A \([\chi_1 = -65.9 (6), \chi_2 = 68.7 (6)^\circ]\).

Introduction. In the crystal structures of cyclo(N-Me-L-Phe)\textsubscript{2} (Benedetti, Marsh & Goodman, 1976) and cyclo(L-Phe)\textsubscript{2} (Gdaniec & Liberek, 1986) none of the molecules adopts a conformation with \(C_2\) symmetry postulated on the basis of NMR data (Kopple & Marr, 1967; Deslauries, Grzonka, Schauburg, Shiba & Walter, 1975). Introduction of a methyl group at one of the 2,5-piperazinedione (hereafter DKP) N atoms destroys the potential symmetry and makes the two phenylalanine residues nonequivalent. \(1^H\) NMR data of such monomethylated cyclic dipeptides (Liberek, Bednarek, Kitowska & Macikowska, 1977) speak in favour of a conformation in which the DKP ring is boat, the aromatic ring of the N-methylamino-acid residue bends over the DKP nucleus and the other aromatic ring is extended towards the N atom.

The crystal structure of cyclo(N-Me-L-Phe-L-Phe) has been solved to find out if the preference of an N-methylamino-acid residue to fold over the DKP ring is preserved in the solid state as well as to provide more structural data on cyclic dipeptides with two aromatic amino-acid residues.

Experimental. Colourless crystal 0.1 x 0.2 x 0.3 mm from methanol–water, \(D_m\) not determined, Syntex P\textsubscript{2}, diffractometer, graphite monochromator, lattice parameters from 15 reflections in 2\(\theta\) 13–22°, profiles measured for 2563 unique reflections with 219< 115° (h 0–11, k 0–14, l 0–26), \(\omega–2\theta\) scan technique, variable scan rate, profile analysis according to Lehmann & Larsen (1974), no significant intensity variation for two standard reflections, absorption ignored, 1697 reflections with \(I > 1.96\sigma(I)\). Structure solved by direct methods with SHELX76 (Sheldrick, 1976), full-matrix least-squares refinement on \(F\), \(w = 1/\sigma^2\), H atoms bonded to C in calculated positions, H atoms bonded to N located on a \(\Delta F\) map, final refinement: anisotropic non-H atoms and empirical isotropic extinction parameter \(x\) used to correct \(F_c\) according to \(F_c' = F_c(1-xF_c^2/\sin\theta)\), \(x\) converged at 1.15 (3) x 10\textsuperscript{-6}; \(R = 0.052\) and \(wR = 0.046; S = 3.09; in final refinement cycle max. \(\Delta\sigma \leq 0.1\), largest peak in final \(\Delta F\) map 0.14, largest hole -0.16 e Å\textsuperscript{-3}; atomic scattering factors from International Tables for X-ray Crystallography (1974); computer programs: SHELX76.
Table 1. Molecular dimensions in Table 2.* Fig. 1

Table 2. Molecular dimensions

(a) Bond lengths (Å)

(b) Bond angles (°)

(c) Torsion angles (°)
One of the aspects of cyclic dipeptide structures is the conformation of the DKP ring. The planarity of the cis peptide bond makes the boat or planar conformation of the DKP ring most probable. However, steric interactions between substituents on DKP as well as some deviations from 0° of the peptide ω torsion angle (torsion-angle nomenclature according to IUPAC–IUB Commission on Biochemical Nomenclature, 1970) give rise to other types of ring buckling. In cyclo(l-Phe)₂, where both peptide bonds are planar, the DKP ring takes the form of a flattened boat $B_{C_1C_2}$ (notation proposed by Boyens, 1978) with Cᵦ atoms in pseudo-axial positions. Substitution of the piperazine N atoms with alkyl groups introduces some strain to the molecule and flattens the potential-energy minimum about the planar conformation of the peptide group. This, in consequence, allows for larger deviations from 0° of the ω torsion angle (Benedetti et al., 1976). In cyclo(N-Me-l-Phe)₂ the ω torsion angles have values of -14 and -7° and the DKP ring takes the form of a twisted boat $N_{T_{C_5}}$ (Benedetti et al., 1976). In the present cyclo(N-Me-l-Phe-l-Phe) with only one tertiary N atom present, two different types of conformation of the DKP ring are observed. From the Cremer & Pople (1975) puckering parameters (Table 3) it can be inferred that in molecule A [ω₁ = -4.4 (7), ω₂ = 4.2 (7)°] the central ring takes a form intermediate between boat $B_{C_1C_2}$ and envelope $E_{C_2}$ with Cᵦ pseudoaxial while in molecule B where the ω angle of the methylated peptide unit is 10.3 (7)° and the other peptide unit is planar [ω₂ = 1.7 (7)°] the conformation is intermediate between twist boat $T_{C_5}$ and boat $B_{C_1C_2}$.

Another interesting feature of the cyclo(N-Me-l-Phe-l-Phe) structure is the distance of one of the methylene protons of the Phe residue in extended conformation to the mean plane through the phenyl ring of the second residue (in folded conformation). The distance is very similar in molecule A (2.60 Å) and molecule B (2.68 Å) and in cyclo(l-Phe)₂ (2.62 Å) and may indicate that there is some kind of interaction between the methylene proton and the π electron cloud of the phenyl ring.

This work was partially supported by the project RP.II.13.2.13.

**Table 3. The Cremer & Pople (1975) puckering parameters of the DKP ring**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>q₂ (Å)</th>
<th>φ₂ (Å)</th>
<th>Q (Å)</th>
<th>φ₂ (°)</th>
<th>β₂ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.183 (7)</td>
<td>0.035 (6)</td>
<td>0.186 (7)</td>
<td>58 (2)</td>
<td>79 (2)</td>
</tr>
<tr>
<td>B</td>
<td>0.199 (4)</td>
<td>0.025 (4)</td>
<td>0.202 (4)</td>
<td>40 (1)</td>
<td>100 (1)</td>
</tr>
</tbody>
</table>

**References**


**Structure of the 2,5-Dimethyl Ether of Avarol,* a Sesquiterpenoid Hydroquinone from the Marine Sponge* Dysidea avara**

**BY FEDERICO GIORDANO**

*Dipartimento di Chimica dell'Università di Napoli, Via Mezzocannone n. 4, 80134 Napoli, Italy*

**AND RAFFAELLA PULITI**

*Istituto per la Chimica di Molecole di Interesse Biologico, CNR, Via Toiano 2, 80072 Arco Felice, Napoli, Italy*

(Received 12 September 1986; accepted 23 December 1986)

**Abstract.** C_{23}H_{34}O_{2}, M_r = 342.53, monoclinic, P2_1, a = 17.200(9), b = 6.599(4), c = 19.316(12) Å, β = 111.67(4)°, V = 2037(2) Å³, Z = 4, D_x = 1.12 Mg m⁻³, λ(Cu Kα) = 1.5418 Å, μ(Cu Kα) = 0.50 mm⁻¹, F(000) = 752, room temperature, final R = 0.056 for 2825 independent observed reflections and 451 parameters. The two independent molecules in the asymmetric unit show identical features except for the different orientation of the hydroquinone fragment with respect to the C_{15} sesquiterpene moiety, due to crystal packing requirements. Of the two trans-connected six-carbon-atom rings forming the sesquiterpene system the cyclohexene ring A has a conformation intermediate between the sofa and half-chair forms, while the cyclohexane ring B shows a slightly distorted chair conformation.

**Introduction.** The title compound is the 2,5-dimethyl ether of avarol, a sesquiterpenoid hydroquinone extracted from the sponge* Dysidea avara* (Minale, Riccio & Sodano, 1974). Its absolute stereochemistry has been stated by De Rosa, Minale, Riccio & Sodano (1976) by spectroscopic and chemical methods. Some doubts about the correctness of these assignments were raised by Djura, Stierle, Sullivan, Faulkner, Arnold & Clardy (1980), owing to the inconsistency of physical data reported for a reaction product common to two different chemical pathways starting from avarol and aureol. Recently, Cariello, De Nicola Giudici & Zanetti (1980) have reported that avarol is active in inducing development aberrations in sea-urchin eggs.

**Experimental.** Needle-shaped crystal (from ethanol), elongated along b, 0.5 × 0.12 × 0.12 mm, Enraf-Nonius CAD-4 diffractometer, Ni-filtered Cu Kα radiation, cell dimensions determined by a least-squares procedure applied to the setting angles of 20 reflections in the θ range 10 ≤ θ ≤ 13°. 2825 unique observed reflections [I_o > 3σ(I_o)] out of the total 3784 measured by the ω/θ scan technique with θ ≤ 65°, 0 ≤ h ≤ 19, 0 ≤ k ≤ 7, −21 ≤ l ≤ 21. Three monitoring reflections, intensity variation < 4%. Lp correction, absorption ignored. Structure solved by direct methods: MULTAN78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Full-matrix least squares

© 1987 International Union of Crystallography