

***tert*-Butoxycarbonyl- α -methyl-L-phenylalanyl-L-valine Benzyl Ester**

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Abstract. Boc-Phe(α -Me)-Val-OBzl, $C_{27}H_{36}N_2O_5$, monoclinic, $P2_1$, $a = 6.083$ (1), $b = 16.550$ (1), $c = 13.277$ (1) Å, $\beta = 93.29$ (1)°, $V = 1334.5$ (2) Å³, $Z = 2$, $M_r = 468.65$, $D_c = 1.166$ Mg m⁻³; $R = 0.047$ for 2652 reflections with $I > 2\sigma(I)$. α -Methyl substitution of phenylalanine forces the backbone into a conformation similar to the preferred conformation of α -aminoisobutyrate [$\varphi = 59.0$ (2)°, $\psi = 33.3$ (2)°], but does not affect the side chain. Intermolecular hydrogen bonds connect the molecules in chains parallel to the a axis.

Introduction. α -Methyl substitution of amino acids which are incorporated into peptides severely limits the conformational freedom of the polypeptide chain. For example, alanine, with its single methyl side chain, is found to exist in a wide variety of conformations, while aminoisobutyrate (Aib) or α -methylalanine show a highly preferred conformation. 16 of the 17 crystallographic observations of aminoisobutyrate incorporated into various peptides fall in the same region of conformational space (Smith *et al.*, 1981). In this way, α -methyl substitution provides a convenient means for examining conformational space as a function of the activity of peptide hormones.

Since the observed conformations of the side chains of many amino acids seem to lie in a very narrow range (Benedetti, 1977), it is also of considerable interest to learn the extent to which α -methyl substitution affects the conformations of these side chains.

We report here the first example of the structure of a peptide containing α -methylphenylalanine [Phe(α -Me)].

Single crystals of Boc-Phe(α -Me)-Val-OBzl (Gorin, Balasubramanian, Cicero, Schwietzen & Marshall, 1980) were grown by slow evaporation of an acetonitrile–water solution. A crystal with approximate dimensions $1.0 \times 0.30 \times 0.08$ mm was used for the data collection. The data were measured on an Enraf–Nonius CAD-4 diffractometer operated in the $\theta/2\theta$ scan mode using Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å). The intensities of 2849 independent reflections with $\sin \theta/\lambda \leq 0.625$ Å⁻¹ were measured. Of

these, 197 reflections had $I \leq 2\sigma(I)$ and were considered unobserved. The intensities were corrected for Lorentz and polarization factors, but not for absorption or extinction. Real and imaginary dispersion-correction factors were applied to the atomic scattering factors (*International Tables for X-ray Crystallography*, 1974). The structure was solved by

Table 1. Atomic coordinates ($\times 10^4$) and B_{eq} ($\times 10$) (Willis & Pryor, 1975) of the nonhydrogen atoms

	x	y	z	B_{eq} (Å ²)
O(1)	−65 (2)	6407	−1450 (1)	40(1)
O(3)	3282 (3)	5581 (1)	−3414 (1)	48 (1)
O(4)	6749 (2)	5109 (1)	−3027 (1)	44 (1)
C(2 γ 2)	2887 (5)	3636 (2)	−1167 (2)	54 (1)
N(1)	5455 (2)	6092 (1)	−2121 (1)	29 (1)
N(2)	2274 (2)	5394 (1)	−1044 (1)	32 (1)
O(2'')	334 (2)	5599 (1)	749 (1)	46 (1)
C(10)	5010 (3)	5598 (1)	−2917 (2)	31 (1)
O(2')	−2859 (2)	5157 (1)	1 (1)	47 (1)
C(2 α)	553 (3)	4844 (1)	−759 (2)	31 (1)
C(1)	1818 (3)	6126 (1)	−1415 (1)	30 (1)
C(1 γ)	4726 (4)	7873 (2)	−2778 (2)	38 (1)
C(2)	−875 (3)	5223 (2)	29 (2)	36 (1)
C(1 β 1)	2970 (3)	7279 (2)	−2516 (2)	36 (1)
C(1 ϵ 2)	6383 (8)	9198 (2)	−2602 (3)	81 (1)
C(1 α)	3798 (3)	6631 (1)	−1735 (1)	28 (1)
C(2 β)	1577 (4)	4040 (2)	−365 (2)	38 (1)
C(1 δ 1)	6364 (5)	7662 (2)	−3420 (2)	52 (1)
C(1 δ 1)	4752 (6)	8649 (2)	−2382 (3)	60 (1)
C(1 ϵ 1)	8010 (5)	8213 (3)	−3637 (2)	72 (1)
C(1 ξ)	7992 (6)	8970 (3)	−3236 (3)	81 (1)
C(4)	757 (5)	6301 (2)	2311 (2)	49 (1)
C(5)	2712 (6)	6664 (3)	2067 (2)	62 (1)
C(2 γ 1)	−190 (6)	3477 (2)	−6 (3)	66 (1)
C(11)	6917 (4)	4612 (2)	−3938 (2)	44 (1)
C(3)	−879 (5)	5988 (3)	1518 (2)	61 (1)
C(9)	343 (7)	6224 (3)	3318 (2)	68 (1)
C(1 β 2)	4823 (3)	7029 (1)	−780 (2)	33 (1)
C(6)	4236 (7)	6940 (3)	2817 (3)	70 (1)
C(8)	1859 (9)	6503 (4)	4059 (3)	85 (1)
C(13)	9004 (6)	4117 (3)	−3672 (4)	84 (1)
C(14)	5020 (5)	4047 (2)	−4100 (3)	68 (1)
C(7)	3780 (8)	6861 (3)	3796 (3)	75 (1)
C(12)	7217 (10)	5160 (4)	−4795 (3)	127 (2)

Standard deviations are in parentheses.

direct methods, using the program *QTAN* (Langs & DeTitta, 1975). The structure was refined by full-matrix least squares minimizing the function $\sum w\Delta F^2$, where $w = 1/\sigma^2(F)$, $\sigma^2(F) = (k/4LpI)[\sigma^2(I) + (0.06I)^2]$ for the observed reflections and $w = 0$ for the others. The y coordinate of atom O(1) was held fixed in order to define the origin in the polar space group. Although a difference map calculated at the end of the isotropic refinement revealed the positions of all but the tertiary butyl-group H atoms, H contributions to the structure factors during the subsequent anisotropic refinement were based upon positions calculated from geometrical considerations. Those H atoms found in the difference map were refined after the latter refinement had converged. The standard deviation of an observation of unit weight is 1.686. The final value of the weighted residual is 0.060. The unweighted residuals for the observed reflections and for all reflections are 0.047 and 0.054 respectively. The atomic coordinates for the nonhydrogen atoms are listed in Table 1.*

Discussion. The structural formula and the bond lengths and angles are shown in Fig. 1. The conventions proposed by the IUPAC-IUB Commission on Biochemical Nomenclature (1970) are used for the numbering of the amino acid atoms and the description of the peptide conformation. The bond lengths and angles do not deviate from those expected for a

peptide (Benedetti, 1977), although some of the terminal bonds appear shortened because of thermal motion. One of the carbonyl bonds [C(1)—O(1)] is longer by eight standard deviations than the other two bonds, which may be a consequence of its role as an acceptor in a strong hydrogen bond.

The molecular conformation is shown in Fig. 2, and the torsion angles are listed in Table 2. The backbone conformation of the valine residue corresponds to the α -helix conformation. Fig. 3 shows a comparison of the ϕ, ψ angles observed for the α -methyl-L-phenylalanine residue with values commonly observed for phenylalanine and the average values of the ϕ, ψ angles for aminoisobutyrate in linear peptides. This average Aib conformation of $(\phi, \psi) = (\pm 55.4, \pm 35.2^\circ)$ corresponds to the minimum-energy conformation obtained from theoretical calculations by Marshall & Bosshard (1972) and is located in the region between the α - and 3_{10} -helix conformations. The 16 observed conformations are within the ranges $|\phi| = 44.3$ to 71.7° and $|\psi| = 11.0$ to 46.1° (Smith *et al.*, 1981). The backbone conformation of α -methyl-L-phenylalanine observed in this

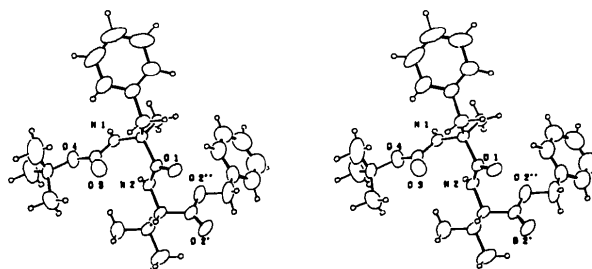


Fig. 2. Observed conformation of Boc-Phe(α -Me)-Val-OBzl.

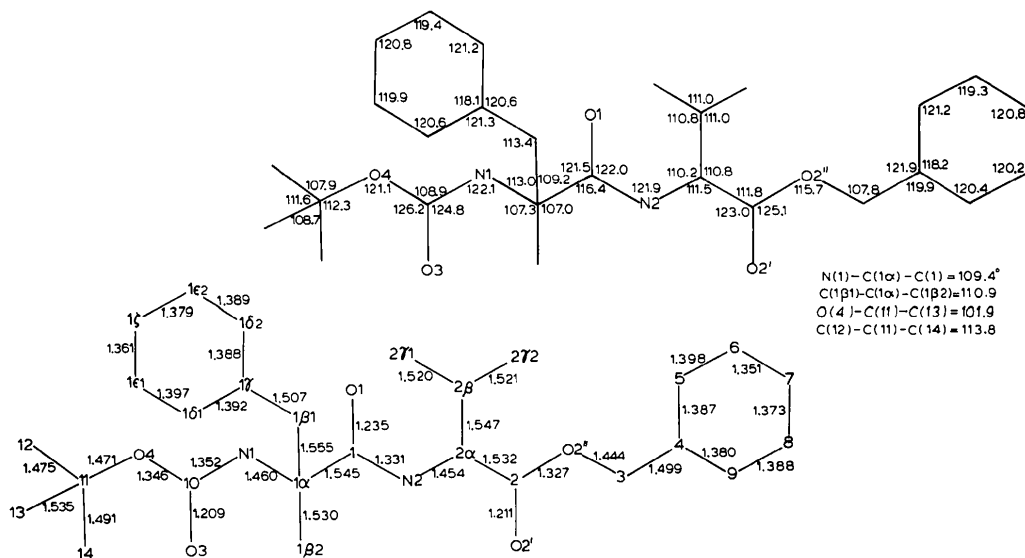


Fig. 1. Structural formula, numbering scheme and bond lengths (Å) and angles (°) for Boc-Phe(α -Me)-Val-OBzl. Standard deviations range from 0.002 to 0.007 Å for the bond lengths and from 0.1 to 0.4° for the bond angles.

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36091 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

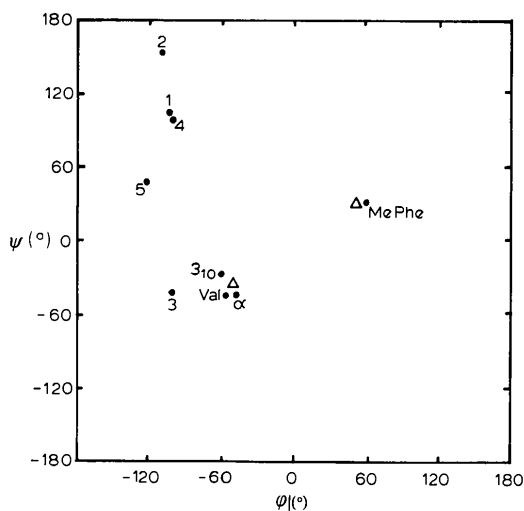


Fig. 3. Diagram of ϕ versus ψ . Val = observed conformation of valine, this study. MePhe = observed conformation of Phe(α -Me), this study. Δ = average value for observed Aib conformation (Smith *et al.*, 1981). α = α -helix conformation. 3_{10} = 3_{10} -helix conformation. (1)–(5) observed conformation of phenylalanine: (1) *N*-Ac-L-Phe-NHMe (Harada & Iitaka, 1977); (2) *N*-Ac-L-Phe-L-Tyr-OH (Stenkamp & Jensen, 1973); (3) L-Pro-L-Phe-OMe.HBr (Sabesan & Venkatesan, 1961); (4)–(5) *N*-chloro-Ac-L-Phe-L-Phe-OEt (Wei, Doherty & Einstein, 1972).

structure does not correspond to any of the conformations observed for Phe residues but falls in the region of the left-handed helices and coincides with the observed Aib conformation. This is a result of short intramolecular contacts involving C(1 β 2) in both the extended ($-120, 100^\circ$) and right-handed α -helix ($-50, -55^\circ$) conformations common for Phe residues. These contacts are relieved by the change in the backbone to the minimum-energy conformation for Aib residues. Thus, it would appear that introduction of a second substituent on the α -carbon of an amino acid has a greater effect on the backbone conformation than the bulk of the side chain.

However, the side-chain conformation is not affected by the α -substitution as the torsion angles χ_1^1, χ_1^2 , and χ_2^1 correspond to those most commonly observed for L-phenylalanine and valine residues respectively (Benedetti, 1977).

This crystal structure also confirms the chemical assignment (Terashima, Achiwa & Yamado, 1966) of the absolute configuration of α -methyl-L-phenylalanine which was resolved by enzymatic digestion (Turk, Panse & Marshall, 1975). The known α -carbon configuration of the L-valine residue establishes the configuration of the entire molecule and therefore confirms the chirality of the α -carbon of Phe(α -Me).

Intermolecular hydrogen bonds connect the molecules in chains parallel to the *a* axis. Hydrophobic channels between these chains contain the Boc group, the phenyl rings and the isopropyl group of the valine

Table 2. Torsion angles ($^\circ$) with standard deviations in parentheses

The torsion angle ω_0 measures the rotation about the urethane bond which links the peptide to Boc [C(1 α)-N(1)-C(10)-O(5)]

	$i = 1$	$i = 2$	$i = 0$
ϕ_i	59.0 (2)	-57.2 (2)	—
ψ_i	33.3 (2)	-44.2 (2)	—
ω_i	-177.1 (2)	179.0 (2)	-172.9 (2)
χ_1^1	-65.5 (2)	176.7 (2)	—
χ_2^1	76.2 (3)	—	—
$\theta_1 = [C(11)-O(4)-C(10)-N(1)]$			-168.5 (2)
$\theta_2 = [C(12)-C(11)-O(4)-C(10)]$			67.4 (3)
$\theta_3 = [C(2)-O(2'')-C(3)-C(4)]$			174.3 (2)
$\theta_4 = [O(2'')-C(3)-C(4)-C(5)]$			40.7 (4)

residue, but no short contacts between these groups are observed. One strong intermolecular hydrogen bond is observed in which N(1) donates a proton to O(1) of the molecule translated in the $+x$ direction [N(1) \cdots O(1), 2.866 (2); H(1) \cdots O(1), 2.03 (2) Å; N(1)-H(1) \cdots O(1), 167 (2) $^\circ$]. A contact is also observed between N(2) and O(2') ($+x$). The geometry of the contact is favorable for hydrogen bonding [N(2)-H(2) \cdots O(2'), 163 (2) $^\circ$], although the distances [N(2) \cdots O(2'), 3.221 (2); H(2) \cdots O(2'), 2.45 (3) Å] indicate it to be very weak. Thus, both H-atom donors are involved in interactions, as is expected, but the intramolecular constraints do not allow them both to be strong hydrogen bonds.

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5(S)-Cyano-9-oxotricyclo[4.2.1.1^{4,7}]dec-2-en-8-yl Methanesulfonate*

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Abstract. C₁₂H₁₃NO₄S, $M_r = 267.3$, orthorhombic, $Pca2_1$, $a = 10.159(5)$, $b = 8.656(3)$, $c = 13.950(5)$ Å, $Z = 4$, $D_m = 1.43$, $D_c = 1.45$ Mg m⁻³. The structure was solved by the Patterson search method and refined to $R = 0.054$ for 960 reflections. No hydrogen bonding is observed and the structure is held together by van der Waals interactions.

Introduction. The compound, supplied by Goverdhan Mehta (University of Hyderabad, Hyderabad, India), is formed in an unanticipated rearrangement pathway from pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione to new C₁₀ carbocyclic systems under Schmidt reaction conditions (Goverdhan Mehta *et al.*, 1977). Spectral data could not reveal the exact nature of the carbocyclic framework of this compound. The preparation, the initial survey of crystals, and the solution and the refinement of the structure have been carried out at Bangalore, India. The intensity data were collected at Texas Christian University, USA.

Preliminary data for the title compound were obtained from Weissenberg photographs taken about different crystallographic axes with Cu $K\alpha$ radiation. The systematic absences, $h0l: h = 2n + 1, 0kl: l = 2n + 1$, indicated the space group $Pca2_1$. The density of the crystal was determined by flotation using aqueous potassium iodide.

Intensity data were collected on a Syntex P2₁ diffractometer with the θ - 2θ scanning technique, using

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a variable scan speed, Cu $K\alpha$ radiation and a graphite monochromator ($\lambda = 1.54178$ Å). The data were corrected for Lorentz and polarization effects, but no correction was made for absorption [$\mu(\text{Cu } K\alpha) = 2.37$ mm⁻¹]. Out of 1190 possible reflections with $2\theta \leq 140^\circ$, 960 were observed and the rest were treated as unobserved [$I < 3\sigma(I)$]. The data were placed on an approximately absolute scale using the Wilson plot. The overall isotropic thermal parameter was 4.73 Å².

Attempts were made to determine the structure using the heavy-atom method [*MULTAN* (Germain, Main & Woolfson, 1971) and *SHELX* (Sheldrick, 1976)]. Since the electron density maps showed mirror-image peaks and spurious peaks, the positions of the light atoms could not be derived. A sharpened Patterson function was computed using *SHELX*, the heavy-atom coordinates were calculated from the heavy-atom vectors (Buerger, 1959), and a search was made for the methanesulfonate fragment by collecting heavy-atom vectors within 2 Å of the origin. Some spurious peaks were eliminated by checking the S vectors in the Patterson map. With the methanesulfonate fragment in the difference map the remaining atoms were determined. Structure factor calculations based on these atoms gave $R = 0.27$.

Block-diagonal least-squares refinement of an overall scale factor, positional coordinates and isotropic temperature factors reduced R to 0.12. A difference Fourier map computed at this stage revealed the locations of the H atoms. Refinement of the positional and anisotropic thermal parameters of the non-hydrogen atoms, with the H atoms included for structure factor calculations only, resulted in a final R