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Crystal Structure and Conformation of *N*-(*t*-Butoxycarbonyl)-L-Alanyl-*S*-Benzyl-L-Cysteine Methyl Ester

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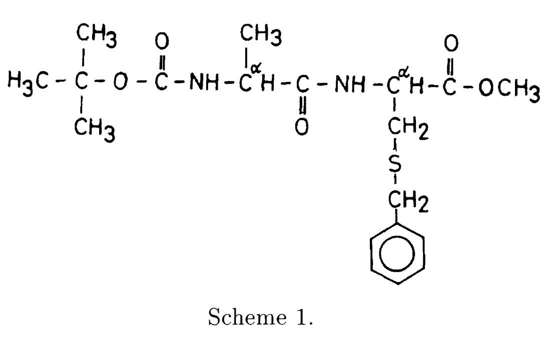
Synopsis. The dipeptide, *N*-(*t*-butoxycarbonyl)-L-alanyl-*S*-benzyl-L-cysteine methyl ester (Boc–Ala–Cys(Bzl)–OMe) has been crystallized in orthorhomic space group $P2_12_12_1$ with cell dimensions of $a=9.565(1)$, $b=43.282(1)$, and $c=5.096(1)$ Å. The structure was determined by direct methods and refined to an R-factor of 0.049. The molecules are packed in a *parallel-pleated sheet* arrangement and stabilized by N–H$\cdots$O hydrogen bonds.

A statistical approach to data analysis reveals that Ala, Val, Leu, Ile, and Cys have a high probability of forming a β-sheet conformation.[1] The results obtained from the analysis of protein structures predict that Ala, Val, Leu, and Ile are the major constituents of the β-strands.[2] In view of these facts, an X-ray study of the Ala–Cys(Bzl) dipeptide was undertaken to determine its adopted conformation (Scheme 1).



Scheme 1.

Experimental

Single crystals of Boc–Ala–Cys(Bzl)–OMe were grown in an aqueous methanol solution. A colorless crystal of approximate dimensions 0.15×0.15×0.3 mm, mounted on a glass fiber, was used for intensity data collection. Twenty-five well-defined reflections ($20°\leq 2\theta \leq 55°$) were used for a least-squares fit to determine the accurate cell constants. The crystal data are $a=9.565(1)$, $b=43.282(3)$, $c=5.096(1)$ Å, and $V=2109.7$ Å^3. There are four molecules of the dipeptide ($C_{15}H_{28}N_2O_5S_2$, $M_r=380.51$) in the unit cell with $D_{calcd}=1.10$ g cm^{-3}, $F(000)=752$, and $\mu=15.2$ cm^{-1}. Intensity data were measured at room temperature (296 K) on an Enraf–Nonius CAD4 diffractometer equipped with graphite monochromated Cu $K\alpha$ ($\lambda=1.5418$ Å) radiation using a variable speed ω–2θ scan technique. Reflections (2416) were collected in the 2θ range 2°—140°. Three reflections monitored as intensity standards for every two hours of X-ray exposure from the beginning to the end of data collection; they showed no significant variation in intensity. Data were corrected for Lorentz and polarization effects, and an empirical absorption correction based on a series of Psi (Ψ) scans of three reflections with $\chi\approx 90°$ was applied. Relative transmission coefficients ranged from 0.85 to 0.99 with an average value of 0.92.

The crystal structure was solved by direct methods using SHELXS86.[3] The best E-map revealed the positions of all 24 non-hydrogen atoms. All non-hydrogen atoms were refined by full-matrix least-squares procedures with isotropic temperature factors initially and then with anisotropic displacement parameters using the SDP package.[4] The H-atom positions were found directly from successive difference Fourier maps and refined isotropically. The refinement converged $[(\Delta/\sigma)_{max}=0.03]$ to values of the standard crystallographic agreement factors of $R=0.049$ and $wR=0.064$ for 2093 observations with $I\geq 3\sigma(I)$ and 349 parameters. A sigma weighting scheme, $w=1/\sigma(F^2)$, where $\sigma(F^2)=\{\sigma^2(I)+0.04I^2\}^{1/2}$, was used. A final difference Fourier map computed at this stage showed maximum and minimum residual electron density values of ± 0.38e Å^{-3}. Atomic scattering factors were taken from International Tables for X-Ray Crystallography (1974).[5] All calculations were performed by using MicroVAX II and VAX730 computers.

Results and Discussion

Figure 1 shows a schematic view of the molecule with atoms numbered. The positional coordinates of the non-hydrogen atoms are given in Table 1.[6] The bond lengths and bond angles are listed in Table 2. The C–S bond length and C–S–C bond angle are in accordance with the average values reported elsewhere.[7—11] The bond lengths and bond angles of the peptide unit are in agreement with the average values found in the literature.[12,13] The selected torsion angles (IUPAC-IUB, 1970)[14] around the various single bonds of the structure are given in Table 3.

The peptide is in the *trans* conformation [$\omega=-173.4(3)°$] and shows significant deviation from planarity [$\Delta\omega=6.6°$]. The internal rotation angles, Φ_1, Ψ_1, Φ_2, Ψ_1^1, and Ψ_1^2, in the peptide backbone are $-130.1(3)°$, $129.3(3)°$, $-148.3(3)°$, $-5.4(4)°$, and $174.8(3)°$, respectively. It has been found from these torsion angles that the molecule takes up an *extended* conformation.

The side chain conformational angles χ_1, χ_2, χ_3, and χ_4, are $74.0(3)°$, $-88.9(3)°$, $-58.0(3)°$, and $118.4(4)°$, respectively. The γ-position sulfur atom is situated in the *gauche* position with respect to both the N2 and the C10 atoms. The deviation of the χ_1 value from 60° ($\Delta\chi=14°$) is due to the steric repulsion between the N2 and S1 atoms. Due to this interaction, the N2–C9–C12 and C9–C12–S1 angles deviate significantly from the

Table 1. Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	$B/\text{Å}^2$
S1	0.16754(9)	0.04464(2)	−0.8237(2)	4.53(2)
O1	0.0979(2)	0.20722(5)	−0.5985(4)	3.88(4)
O2	0.2248(3)	0.19212(6)	−0.9518(5)	5.56(6)
O3	0.3728(3)	0.12276(5)	−0.2591(5)	4.87(5)
O4	0.5389(3)	0.05982(6)	−0.9513(5)	4.60(5)
O5	0.5062(3)	0.02279(5)	−0.6495(5)	4.76(5)
N1	0.2801(3)	0.17658(5)	−0.5394(6)	3.54(5)
N2	0.3961(3)	0.10180(5)	−0.6595(5)	3.32(5)
C1	0.0573(5)	0.24922(8)	−0.9129(8)	5.03(8)
C2	−0.1105(4)	0.2355(1)	−0.5590(9)	6.66(9)
C3	−0.0814(4)	0.19963(9)	−0.9342(9)	4.93(8)
C4	−0.0087(3)	0.22318(7)	−0.7596(6)	3.68(6)
C5	0.2024(3)	0.19184(7)	−0.7172(6)	3.44(6)
C6	0.3971(3)	0.15767(7)	−0.6240(7)	3.80(6)
C7	0.5367(4)	0.17199(9)	−0.551(1)	6.5(1)
C8	0.3857(3)	0.12578(6)	−0.4957(7)	3.38(6)
C9	0.4022(3)	0.07024(6)	−0.5636(6)	3.11(5)
C10	0.4904(3)	0.05122(7)	−0.7483(7)	3.42(6)
C11	0.5781(5)	0.00090(8)	−0.810(1)	6.2(1)
C12	0.2582(3)	0.05558(7)	−0.5257(6)	3.61(6)
C13	0.0719(4)	0.07983(9)	−0.9057(7)	4.75(8)
C14	−0.0256(3)	0.09063(7)	−0.6942(7)	3.80(6)
C15	−0.0073(5)	0.11886(8)	−0.578(1)	5.9(1)
C16	−0.0998(7)	0.12816(9)	−0.381(1)	8.2(1)
C17	−0.2074(5)	0.1095(1)	−0.298(1)	7.5(1)
C18	−0.2230(4)	0.0812(1)	−0.4145(9)	5.82(9)
C19	−0.1348(3)	0.07225(9)	−0.6090(8)	4.52(7)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3)\times[a^2\times B(1,1)+b^2\times B(2,2)+c^2\times B(3,3)+ab(\cos\gamma)\times B(1,2)+ac(\cos\beta)\times B(1,3)+bc(\cos\alpha)\times B(2,3)]$.

regular tetrahedral values. This situation is also found in Boc–Cys(Bzl)– Gly–OMe[7] and Boc–Ile–Cys(Bzl)–OMe.[15] The intramolecular atomic distance between the N2 and S1 atoms is 3.407(5) Å. The torsion angles that characterize the Boc group, ω_0 and θ_0, are −174.2(2)° and 178.4(2)°, respectively, which corresponds to a *trans–trans* conformation.[16]

The packing of molecules down the *a*-axis is shown in Fig. 2. The molecules are held together by N–H···O and C–H···O hydrogen bonds (Table 4) to form parallel pleated sheets. The distance between adjacent chains (5.096(1) Å) is comparable to the theoretically calculated value of 4.85 Å.[16] The molecules are aggregated in a helical fashion along the *b*-axis. The nonpolar

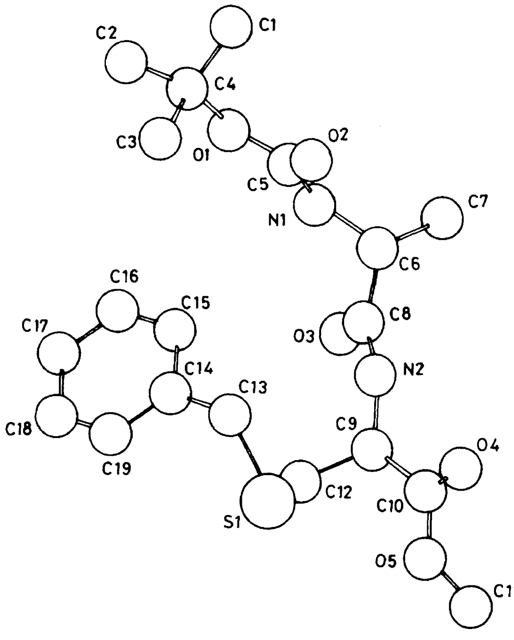


Fig. 1. Schematic representation of the molecule.

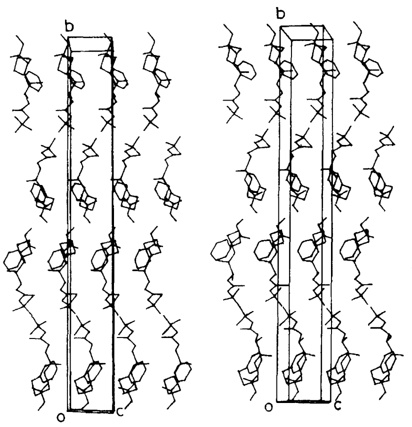


Fig. 2. Stereoview of the packing of the molecules in the unit cell.

Table 2. Molecular Geometry

(a) Bond distances in angstroms

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
S1	C12	1.812(3)	N1	C5	1.345(4)	C9	C10	1.508(4)
S1	C13	1.825(4)	N1	C6	1.452(4)	C9	C12	1.529(4)
O1	C4	1.480(4)	N2	C8	1.335(4)	C13	C14	1.500(5)
O1	C5	1.345(4)	N2	C9	1.452(4)	C14	C15	1.370(5)
O2	C5	1.215(4)	C1	C4	1.510(5)	C14	C19	1.383(5)
O3	C8	1.219(4)	C2	C4	1.509(5)	C15	C16	1.398(8)
O4	C10	1.193(4)	C3	C4	1.521(5)	C16	C17	1.374(7)
O5	C10	1.338(4)	C6	C7	1.519(5)	C17	C18	1.368(7)
O5	C11	1.428(5)	C6	C8	1.531(4)	C18	C19	1.358(6)

(b) Bond angles in degrees

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C12	S1	C13	102.3(2)	O1	C5	N1	110.5(3)	O4	C10	C9	126.0(3)
C4	O1	C5	119.6(2)	O2	C5	N1	124.8(3)	O5	C10	C9	109.3(3)
C10	O5	C11	116.7(3)	N1	C6	C7	112.0(3)	S1	C12	C9	115.7(2)
C5	N1	C6	120.2(3)	N1	C6	C8	109.1(3)	S1	C13	C14	114.0(3)
C8	N2	C9	121.6(3)	C7	C6	C8	109.0(3)	C13	C14	C15	120.7(3)
O1	C4	C1	110.3(3)	O3	C8	N2	122.9(3)	C13	C14	C19	121.1(3)
O1	C4	C2	103.5(3)	O3	C8	C6	121.7(3)	C15	C14	C19	118.3(4)
O1	C4	C3	109.1(3)	N2	C8	C6	115.4(3)	C14	C15	C16	119.2(4)
C1	C4	C2	110.9(3)	N2	C9	C10	109.0(2)	C15	C16	C17	121.6(4)
C1	C4	C3	112.9(3)	N2	C9	C12	113.4(2)	C16	C17	C18	118.4(4)
C2	C4	C3	109.8(3)	C10	C9	C12	110.9(2)	C17	C18	C19	120.2(4)
O1	C5	O2	124.7(3)	O4	C10	O5	124.7(3)	C14	C19	C18	122.3(4)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 3. Selected Torsional Angles in Degrees

	Atom 1	Atom 2	Atom 3	Atom 4	Angle
θ_0	C4	O1	C5	N1	−174.2(2)
ω_0	C6	N1	C5	O1	178.4(2)
ϕ_1	C5	N1	C6	C8	−130.1(3)
ω_1	C9	N2	C8	C6	173.4(3)
ψ_1	N1	C6	C8	N2	129.3(3)
ϕ_2	C8	N2	C9	C10	−148.3(3)
ω_2	C11	O5	C10	C9	175.2(3)
$\psi_1{}^1$	N2	C9	C10	O4	−5.4(4)
$\psi_1{}^2$	N2	C9	C10	O5	174.8(3)
χ_1	N2	C9	C12	S1	74.0(3)
χ_2	C13	S1	C12	C9	−88.9(3)
χ_3	C12	S1	C13	C14	−60.0(3)
χ_4	S1	C13	C14	C15	118.4(4)

Table 4. Lengths (Å) and Angles (°) for Hydrogen Bondings Scheme

D–H···A	D···A	H···A	<D–H···A	Position of acceptor
N1–HN1···O2	3.114(4)	2.30(5)	168(3)	$x, y, z+1$
N2–HN2···O3	3.196(4)	2.57(4)	167(4)	$x, y, z-1$

parts of the molecules are in close proximity with each other, thereby forming a hydrophobic region. There exist stacking interactions between the benzene rings along the *a*-axis. The van der Waals interactions between the hydrophobic regions also play an important role in stabilizing the packing of the molecules.

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