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Structure and molecular modelling of protected dipeptide fragment (Boc–Phe–Leu–OBzl) of enkephalin

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Abstract

The conformational characteristics of a flexible totally protected *C*-terminal dipeptide fragment (Boc–Phe–Leu–OBzl) of enkephalin are studied using X-ray data, molecular modelling and data retrieved from the Cambridge Structural Database. The dipeptide crystallizes with seven conformers in the asymmetric unit. $C_{27}H_{36}N_2O_5$, T = 133 K, monoclinic, $P2_1$, a = 13.706 (3), b = 22.800 (3), c = 30.674 (5) Å, β = 97.15 (3)°, V = 9511 (3) Å^3, Z = 14, D_c = 1.145 Mg m^{-3}. Six of the seven molecules exhibit folded conformations with hydrophobic groups disposed at the opposite side of the peptide backbone. The characteristic Φ_1 and Ψ_1 angles of the Phe residue and Φ_2 of the Leu fragment are in the allowed region defined in the Ramachandran diagram. However, they do not belong to the family of the lowest energy conformations. In the crystal, molecules are interconnected *via* N—H···O hydrogen bonds of peptide groups forming an infinite sheet similar to a parallel β-sheet. Molecular dynamics simulations performed *in vacuo* reproduce the conformers and rotamers detected in the solid state.

1. Introduction

The main goal of the structure–activity relationship studies on bioactive peptides is the understanding of the biological phenomena at the molecular level with the aim of producing and developing materials relevant to pharmacology and medicinal chemistry that might mimic biological processes by enhancing or modulating their effects. In recent years a large number of structures of bioactive peptides and their analogues, synthetic model peptides and various functional derivatives (Marraud & Aubry, 1996) as well as analogues of α-amino acids as intermediates in peptide synthesis (Toniolo *et al.*, 1996), have been determined by X-ray diffraction.

In this paper we present structural studies on a fully blocked dipeptide *N-tert*-butyloxycarbonyl-L-phenylalanyl-L-leucine benzyl ester (Boc–Phe–Leu–OBzl) based on X-ray analysis and molecular modelling (molecular mechanics and molecular dynamics simulations). This dipeptide model representing the *C*-terminal amino acid sequence of the endogenous opioid pentapeptide leucine enkephalin (H–Tyr–Gly Gly Phe–Leu–OH; Lord *et al.*, 1977) is devoid of opioid activity (Schiller, 1984). Recent conformational studies of enkephalin-related peptidomimetics with sequences including –Phe–Leu– indicated the presence of multiple conformers in solution (Čudić *et al.*, 1998). Therefore, it is interesting to see conformational characteristics of the *C*-terminal Phe–Leu dipeptide.

The Cambridge Structural Database (Allen & Kennard, 1993) was used to retrieve the X-ray structures of peptides with the sequence –Phe–Leu– to examine possible conformational preferences.

2. Experimental

Well formed prismatic crystals of size suitable for X-ray data collection were grown from petroleum ether at 277 K over 2 d. Data collection at low temperature using a sealed copper tube with attached scintillation counter did not provide a sufficient number of reflections for structure determination. The size of the unit cell suggested seven molecules in an asymmetric unit. Further crystallization experiments were performed in different solvents in order to prepare crystals with fewer molecules in the asymmetric unit. The dipeptide is not soluble in water. The combinations of solvents used in the experiments were (*a*) diethyl ether + hexane (1:1) and (*b*) diisopropyl ether + hexane (1:2). The crystals obtained from these solvents had the same unit cell as obtained in the first crystallization. Successful data collection was at 133 K on a Huber/Stoe diffractometer with attached Siemens 1K CCD area detector and using an Mo sealed tube. The improvement in the data quality is primarily to be attributed to the use of the CCD detector. Crystallographic data, details of data collection and refinement are listed in Table 1. The structure was solved using a preliminary version of *SHELXD* (Sheldrick, 1997*a*, 1998), which combined 'peak list optimization' (Sheldrick & Gould, 1995) with the 'minimal function' in a procedure different from, but inspired by, the shake-and-bake method of Miller *et al.* (1993, 1994). 1820 large *E*-values were employed and six solutions

Table 1. *Experimental details*

Crystal data	
Chemical formula	$C_{27}H_{36}N_2O_5$
Chemical formula weight	468.58
Cell setting	Monoclinic
Space group	$P2_1$
a (Å)	13.706 (3)
b (Å)	22.800 (5)
c (Å)	30.674 (6)
β (°)	97.15 (3)
V (Å^3)	9511 (3)
Z	14
D_x (Mg m^{-3})	1.145
Radiation type	Mo $K\alpha$
Wavelength (Å)	0.71073
No. of reflections for cell parameters	8192
θ range (°)	1.91–25.0
μ (mm^{-1})	0.079
Max./min. transmission	0.958/0.956
Temperature (K)	133 (2)
Crystal form	Prismatic
Crystal size (mm)	0.58 × 0.55 × 0.55
Crystal colour	Colourless
Data collection	
Diffractometer	Stoe–Siemens–Huber CCD area detector
Data collection method	φ scans
Absorption correction	Semi-empirical from equivalents
T_{min}	0.9558
T_{max}	0.9580
No. of measured reflections	105 749
No. of independent reflections	33 467
No. of observed reflections	29 661
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.0320
θ_{max} (°)	25.00
Range of h, k, l	$-16 \rightarrow h \rightarrow 16$ $-27 \rightarrow k \rightarrow 27$ $0 \rightarrow l \rightarrow 36$
F(000)	3528
Completeness (%)	99.9
Refinement	
Refinement	Full-matrix least-squares on F^2
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0455$, $wR_2 = 0.0962$
R indices (all data)	$R_1 = 0.0569$, $wR_2 = 0.1035$
S	1.129
No. of reflections used in refinement	33 467
No. of parameters used	2101
H-atom treatment	H parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0331P)^2 + 3.52P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001
$\Delta\rho_{max}$ (e Å^{-3})	0.488
$\Delta\rho_{min}$ (e Å^{-3})	−0.216
Extinction method	*SHELXL*97 (Sheldrick, 1997*b*; Sheldrick & Schneider, 1997)
Extinction coefficient	0.00094 (7)
Absolute structure parameter	−0.2 (4)
Source of atomic scattering factors	*SHELXL*97 (Sheldrick, 1997*b*; Sheldrick & Schneider, 1997)

Table 1 (*cont.*)

Computer programs	
Data collection	*SMART* (Siemens, 1997*a*)
Cell refinement	*SAINT* (Siemens, 1997*b*)
Data reduction	*SAINT* (Siemens, 1997*b*)
Structure solution	*SHELXD* (Sheldrick, 1997*a*)
Structure refinement	*SHELXL*97 (Sheldrick, 1997*b*; Sheldrick & Schneider, 1997)
Preparation of material for publication	*SHELXL*97 (Sheldrick, 1997*b*; Sheldrick & Schneider, 1997)

Table 2. *Final atomic coordinates and equivalent isotropic thermal parameters*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
(1)				
C1	0.5390 (2)	0.3633 (1)	0.2939 (1)	0.0401 (6)
C2	0.6020 (2)	0.3362 (1)	0.3327 (1)	0.0559 (8)
C3	0.4326 (2)	0.3452 (1)	0.2942 (1)	0.0496 (7)
C4	0.5773 (2)	0.34823 (8)	0.25095 (7)	0.0552 (8)
O	0.5493 (1)	0.42618 (7)	0.30310 (5)	0.0341 (4)
C5	0.4954 (2)	0.4658 (1)	0.2777 (7)	0.0269 (5)
O_0	0.4571 (1)	0.45733 (7)	0.24025 (5)	0.0346 (4)
N1	0.4907 (1)	0.51590 (8)	0.30012 (6)	0.0243 (4)
C_1^α	0.4334 (2)	0.5662 (1)	0.28209 (7)	0.0252 (5)
C_1^β	0.3697 (1)	0.58919 (6)	0.31536 (5)	0.0292 (5)
C_1^γ	0.2866 (1)	0.54846 (6)	0.32544 (5)	0.0307 (5)
$C_1^{\delta1}$	0.2305 (1)	0.56592 (6)	0.35788 (5)	0.0448 (7)
$C_1^{\varepsilon1}$	0.1525 (2)	0.5305 (2)	0.3677 (1)	0.0572 (8)
C_1^ζ	0.1324 (2)	0.4783 (2)	0.3462 (1)	0.0569 (8)
$C_1^{\varepsilon2}$	0.1887 (2)	0.4615 (1)	0.3140 (1)	0.0507 (7)
$C_1^{\delta2}$	0.2647 (2)	0.4967 (1)	0.30351 (8)	0.0373 (6)
C1′	0.5046 (2)	0.61335 (9)	0.26948 (7)	0.0236 (5)
O1	0.5659 (1)	0.63675 (7)	0.29662 (5)	0.0336 (4)
N2	0.4963 (1)	0.62604 (8)	0.22661 (6)	0.0264 (4)
C_2^α	0.5589 (2)	0.6693 (1)	0.20930 (7)	0.0270 (5)
C_2^β	0.5503 (2)	0.6634 (1)	0.15932 (7)	0.0296 (5)
C_2^γ	0.5928 (2)	0.6069 (1)	0.14249 (8)	0.0316 (5)
$C_2^{\delta1}$	0.5524 (2)	0.5974 (1)	0.09422 (8)	0.0436 (7)
$C_2^{\delta2}$	0.7051 (2)	0.6078 (1)	0.1482 (1)	0.0465 (7)
C2′	0.5301 (2)	0.7311 (1)	0.22098 (7)	0.0295 (5)
O2	0.4508 (2)	0.74596 (8)	0.22825 (7)	0.0487 (5)
O21	0.6065 (1)	0.76712 (7)	0.21938 (6)	0.0403 (4)
C21	0.5849 (2)	0.8299 (1)	0.22151 (9)	0.0452 (7)
C22	0.5485 (2)	0.8533 (1)	0.17684 (9)	0.0374 (6)
C23	0.6070 (2)	0.8496 (1)	0.1430 (1)	0.0429 (6)
C24	0.5763 (2)	0.8738 (1)	0.1024 (1)	0.0476 (7)
C25	0.4871 (2)	0.9020 (1)	0.0952 (1)	0.0488 (7)
C26	0.4278 (2)	0.9052 (1)	0.1281 (1)	0.0463 (7)
C27	0.4580 (2)	0.8805 (1)	0.16856 (9)	0.0418 (6)
(2)				
C1	0.6954 (2)	0.1923 (1)	0.18581 (9)	0.0411 (6)
C2	0.7745 (2)	0.2352 (1)	0.2037 (1)	0.0476 (7)
C3	0.6286 (3)	0.2204 (1)	0.1485 (1)	0.0616 (9)
C4	0.6364 (2)	0.16882 (9)	0.22029 (8)	0.0520 (8)
O	0.7381 (1)	0.14287 (7)	0.16343 (5)	0.0380 (4)
C5	0.8006 (2)	0.1056 (1)	0.18691 (7)	0.0281 (5)
O_0	0.8379 (1)	0.11378 (7)	0.22450 (5)	0.0356 (4)
N1	0.8168 (1)	0.05870 (8)	0.16257 (6)	0.0243 (4)
C_1^α	0.8677 (2)	0.00775 (9)	0.18272 (7)	0.0226 (5)
C_1^β	0.7988 (1)	−0.04517 (6)	0.18110 (4)	0.0276 (5)
C_1^γ	0.7189 (1)	−0.03285 (6)	0.20986 (4)	0.0284 (5)
$C_1^{\delta1}$	0.7381 (1)	−0.04003 (6)	0.25511 (4)	0.0381 (6)
$C_1^{\varepsilon1}$	0.6668 (2)	−0.0242 (1)	0.28157 (9)	0.0540 (8)
C_1^ζ	0.5782 (2)	−0.0013 (2)	0.2634 (1)	0.0587 (9)

Table 2 (*cont.*)

	x	y	z	U_{eq}
$C_1^{\varepsilon 2}$	0.5597 (2)	0.0053 (1)	0.2186 (1)	0.0505 (8)
$C_1^{\delta 2}$	0.6296 (2)	−0.0102 (1)	0.19211 (9)	0.0364 (6)
O1	0.9550 (1)	−0.02370 (8)	0.12301 (5)	0.0354 (4)
C1′	0.9591 (2)	−0.0060 (1)	0.16088 (7)	0.0259 (5)
N2	1.0434 (1)	0.00301 (9)	0.18645 (6)	0.0279 (4)
C_2^{α}	1.1370 (2)	−0.0150 (1)	0.17326 (8)	0.0315 (5)
C_2^{β}	1.2208 (2)	0.0069 (1)	0.20668 (8)	0.0358 (6)
C_2^{γ}	1.2319 (2)	0.0732 (1)	0.2105 (1)	0.0494 (7)
$C_2^{\delta 1}$	1.3006 (3)	0.0884 (2)	0.2519 (1)	0.070 (1)
$C_2^{\delta 2}$	1.2700 (3)	0.0993 (2)	0.1704 (1)	0.080 (1)
C2′	1.1445 (2)	−0.0810 (1)	0.16902 (8)	0.0381 (6)
O2	1.2051 (2)	−0.1045 (1)	0.14986 (8)	0.0670 (7)
O21	1.0784 (1)	−0.10987 (8)	0.18865 (6)	0.0391 (4)
C21	1.0790 (2)	−0.1730 (1)	0.1859 (1)	0.0473 (7)
C22	0.9964 (2)	−0.19620 (8)	0.20889 (6)	0.0370 (6)
C23	0.9583 (2)	−0.25119 (7)	0.19693 (6)	0.0589 (8)
C24	0.8838 (3)	−0.2741 (2)	0.2185 (1)	0.067 (1)
C25	0.8461 (2)	−0.2432 (1)	0.2507 (1)	0.0540 (8)
C26	0.8850 (2)	−0.1886 (1)	0.26280 (9)	0.0458 (7)
C27	0.9596 (2)	−0.1652 (1)	0.24186 (8)	0.0385 (6)
(3)				
C1	0.4978 (2)	0.0792 (1)	0.05025 (8)	0.0348 (6)
C2	0.4958 (2)	0.0754 (1)	0.09953 (8)	0.0424 (7)
C3	0.5464 (2)	0.1346 (1)	0.03685 (9)	0.0451 (7)
C4	0.3946 (1)	0.0734 (1)	0.02632 (8)	0.0475 (7)
O	0.5476 (1)	0.02800 (7)	0.03375 (5)	0.0331 (4)
C5	0.6437 (2)	0.0178 (1)	0.04743 (7)	0.0289 (5)
O_0	0.6912 (1)	0.04255 (8)	0.07838 (5)	0.0395 (4)
N1	0.6799 (1)	−0.02385 (9)	0.02295 (6)	0.0293 (4)
C_1^{α}	0.7843 (2)	−0.0357 (1)	0.03007 (7)	0.0295 (5)
C_1^{β}	0.8093 (1)	−0.9096 (7)	0.00518 (5)	0.0329 (5)
C_1^{γ}	0.7723 (1)	−0.14710 (7)	0.02359 (5)	0.0378 (6)
$C_1^{\delta 1}$	0.8129 (1)	−0.16712 (7)	0.06469 (5)	0.0507 (8)
$C_1^{\varepsilon 1}$	0.7820 (3)	−0.2205 (2)	0.0803 (1)	0.074 (1)
C_1^{ζ}	0.7116 (4)	−0.2527 (2)	0.0557 (2)	0.0992 (2)
$C_1^{\varepsilon 2}$	0.6707 (4)	−0.2328 (2)	0.0151 (2)	0.092 (1)
$C_1^{\delta 2}$	0.7019 (3)	−0.1804 (1)	−0.0009 (1)	0.0596 (8)
C1′	0.8428 (2)	0.0149 (1)	0.01390 (8)	0.0327 (6)
O1	0.8161 (2)	0.04026 (9)	−0.02071 (6)	0.0488 (5)
N2	0.9274 (2)	0.02664 (9)	0.03899 (6)	0.0340 (5)
C_2^{α}	0.9997 (2)	0.0683 (1)	0.02701 (8)	0.0406 (6)
C_2^{β}	1.0343 (2)	0.1097 (1)	0.06548 (9)	0.0459 (7)
C_2^{γ}	0.9529 (2)	0.1356 (1)	0.08914 (9)	0.0439 (7)
$C_2^{\delta 1}$	0.8713 (3)	0.1662 (2)	0.0592 (1)	0.0632 (9)
$C_2^{\delta 2}$	0.9966 (3)	0.1754 (2)	0.1264 (1)	0.0636 (9)
C2′	1.0842 (2)	0.0338 (1)	0.01206 (9)	0.0491 (8)
O2	1.1104 (2)	0.0363 (1)	−0.02366 (7)	0.0770 (7)
O21	1.1245 (2)	−0.0019 (1)	0.04419 (6)	0.0562 (6)
C21	1.1889 (2)	−0.0483 (2)	0.0321 (1)	0.068 (1)
C22	1.1309 (2)	−0.1202 (9)	0.01759 (7)	0.0497 (7)
C23	1.0956 (2)	−0.13790 (9)	0.04873 (7)	0.067 (1)
C24	1.0391 (3)	−0.1871 (2)	0.0348 (1)	0.070 (1)
C25	1.0184 (2)	−0.1999 (2)	−0.0085 (1)	0.065 (1)
C26	1.0539 (2)	−0.1641 (2)	−0.0388 (1)	0.0600 (8)
C27	1.1099 (2)	−0.1153 (1)	−0.0260 (1)	0.0488 (7)
(4)				
C1	0.1025 (2)	1.2479 (1)	0.26940 (9)	0.0424 (7)
C2	0.0860 (3)	1.2687 (1)	0.2219 (1)	0.0616 (9)
C3	0.2105 (2)	1.2513 (1)	0.2868 (1)	0.0590 (8)
C4	0.0386 (2)	1.28065 (9)	0.29705 (9)	0.0544 (8)
O	0.0674 (1)	1.18664 (7)	0.26538 (5)	0.0380 (4)
C5	0.0710 (2)	1.1516 (1)	0.30090 (7)	0.0292 (5)
O_0	0.1213 (1)	1.16002 (8)	0.33602 (5)	0.0392 (4)
N1	0.0125 (1)	1.10479 (8)	0.29155 (6)	0.0263 (4)
C_1^{α}	−0.0027 (2)	1.0622 (1)	0.32494 (7)	0.0243 (5)

Table 2 (*cont.*)

	x	y	z	U_{eq}
C_1^{β}	−0.1116 (1)	1.05814 (6)	0.33262 (5)	0.0290 (5)
C_1^{γ}	−0.1469 (1)	1.11329 (6)	0.35321 (5)	0.0292 (5)
$C_1^{\delta 1}$	−0.1802 (1)	1.16049 (6)	0.32678 (5)	0.0480 (7)
$C_1^{\varepsilon 1}$	−0.2094 (3)	1.2119 (1)	0.3464 (1)	0.0581 (8)
C_1^{ζ}	−0.2074 (2)	1.2157 (1)	0.3910 (1)	0.0481 (7)
$C_1^{\varepsilon 2}$	−0.1741 (2)	1.1696 (1)	0.4167 (1)	0.0503 (8)
$C_1^{\delta 2}$	−0.1439 (2)	1.1184 (1)	0.39803 (8)	0.0400 (6)
C1′	0.0333 (2)	1.0019 (1)	0.31372 (7)	0.0230 (5)
O1	0.0270 (1)	0.98323 (7)	0.27582 (5)	0.0346 (4)
N2	0.0690 (2)	0.97032 (8)	0.34843 (6)	0.0295 (4)
C_2^{α}	0.1103 (2)	0.9117 (1)	0.34666 (8)	0.0320 (5)
C_2^{β}	0.2184 (2)	0.9128 (1)	0.36527 (9)	0.0411 (6)
C_2^{γ}	0.2843 (2)	0.9458 (1)	0.3365 (1)	0.0487 (7)
$C_2^{\delta 1}$	0.3751 (3)	0.9693 (2)	0.3648 (1)	0.075 (1)
$C_2^{\delta 2}$	0.3119 (2)	0.9072 (2)	0.2999 (1)	0.0591 (8)
C2′	0.0537 (2)	0.8677 (1)	0.37101 (8)	0.0333 (6)
O2	0.0924 (1)	0.82689 (8)	0.39117 (7)	0.0541 (5)
O21	−0.0424 (1)	0.87789 (7)	0.36618 (5)	0.0350 (4)
C21	−0.0991 (2)	0.8375 (1)	0.39011 (9)	0.0381 (6)
C22	−0.2083 (1)	0.84985 (8)	0.37841 (6)	0.0413 (6)
C23	−0.2514 (1)	0.89825 (8)	0.39585 (6)	0.0523 (8)
C24	−0.3528 (2)	0.9074 (2)	0.3867 (1)	0.0582 (9)
C25	−0.4082 (2)	0.8680 (2)	0.3599 (1)	0.066 (1)
C26	−0.3665 (2)	0.8205 (2)	0.3420 (1)	0.0623 (9)
C27	−0.2665 (2)	0.8111 (1)	0.35194 (9)	0.0489 (7)
(5)				
C1	0.6027 (2)	0.4000 (1)	0.09507 (9)	0.0425 (7)
C2	0.6900 (2)	0.3846 (1)	0.1285 (1)	0.0613 (9)
C3	0.5468 (2)	0.3454 (1)	0.0782 (1)	0.0527 (8)
C4	0.6344 (2)	0.4364 (1)	0.05781 (5)	0.068 (1)
O	0.5430 (1)	0.43575 (8)	0.12159 (6)	0.0380 (4)
C5	0.4532 (2)	0.4541 (1)	0.10430 (8)	0.0293 (5)
O_0	0.4176 (1)	0.44754 (8)	0.06641 (5)	0.0384 (4)
N1	0.4090 (1)	0.48256 (8)	0.13539 (6)	0.0272 (4)
C_1^{α}	0.3070 (2)	0.5002 (1)	0.12604 (7)	0.0253 (5)
C_1^{β}	0.2418 (1)	0.46575 (7)	0.15488 (5)	0.0335 (6)
C_1^{γ}	0.2467 (1)	0.40000 (7)	0.14689 (5)	0.0337 (6)
$C_1^{\delta 1}$	0.1831 (1)	0.37421 (7)	0.11350 (5)	0.0398 (6)
$C_1^{\varepsilon 1}$	0.1923 (2)	0.3149 (1)	0.1051 (1)	0.0511 (7)
C_1^{ζ}	0.2627 (2)	0.2812 (1)	0.1291 (1)	0.0551 (8)
$C_1^{\varepsilon 2}$	0.3252 (3)	0.3068 (1)	0.1620 (1)	0.0584 (8)
$C_1^{\delta 2}$	0.3166 (2)	0.3660 (1)	0.17089 (9)	0.0474 (7)
C1′	0.2949 (2)	0.5653 (1)	0.13446 (7)	0.0256 (5)
O1	0.3261 (1)	0.58761 (7)	0.16999 (5)	0.0340 (4)
N2	0.2455 (1)	0.59503 (8)	0.10116 (6)	0.0280 (4)
C_2^{α}	0.2042 (2)	0.6530 (1)	0.10558 (8)	0.0306 (5)
C_2^{β}	0.2196 (2)	0.6931 (1)	0.06732 (8)	0.0350 (6)
C_2^{γ}	0.3231 (2)	0.7182 (1)	0.06867 (9)	0.0387 (6)
$C_2^{\delta 1}$	0.3482 (2)	0.7593 (1)	0.1078 (1)	0.0521 (8)
$C_2^{\delta 2}$	0.3325 (2)	0.7507 (1)	0.0259 (1)	0.0560 (8)
C2′	0.0954 (2)	0.6493 (1)	0.11088 (9)	0.0427 (6)
O2	0.0406 (2)	0.6901 (1)	0.10731 (9)	0.0721 (7)
O21	0.0700 (1)	0.59598 (9)	0.12270 (9)	0.0661 (7)
C21	−0.0329 (2)	0.5878 (2)	0.1298 (2)	0.083 (1)
C22	−0.0346 (2)	0.5310 (1)	0.15323 (8)	0.0513 (8)
C23	−0.0083 (2)	0.52908 (9)	0.19846 (8)	0.098 (2)
C24	−0.0045 (4)	0.4763 (4)	0.2195 (2)	0.135 (3)
C25	−0.0266 (3)	0.4254 (3)	0.1964 (2)	0.110 (2)
C26	−0.0523 (3)	0.4275 (2)	0.1529 (2)	0.074 (1)
C27	−0.0561 (2)	0.4803 (1)	0.1311 (1)	0.0533 (8)
(6)				
C1	0.4789 (2)	0.4549 (1)	0.45905 (9)	0.0468 (7)
C2	0.4446 (2)	0.4435 (1)	0.5036 (1)	0.0541 (8)
C3	0.3934 (3)	0.4499 (2)	0.4229 (1)	0.085 (1)
C4	0.5615 (2)	0.41470 (8)	0.4510 (1)	0.082 (1)

Table 2 (*cont.*)

	x	*y*	*z*	U_{eq}
O	0.5132 (1)	0.51572 (8)	0.46340 (5)	0.0390 (4)
C5	0.5508 (2)	0.5421 (1)	0.42988 (7)	0.0302 (5)
O_0	0.5536 (1)	0.52061 (7)	0.39369 (5)	0.0383 (4)
N1	0.5845 (2)	0.59553 (9)	0.44107 (6)	0.0312 (4)
C_1^α	0.6274 (2)	0.6304 (1)	0.40873 (7)	0.0265 (5)
C_1^β	0.6425 (1)	0.69387 (6)	0.42459 (5)	0.0314 (5)
C_1^γ	0.5475 (1)	0.72774 (6)	0.42597 (5)	0.0313 (5)
$C_1^{\delta1}$	0.4782 (1)	0.73169 (6)	0.38893 (5)	0.0395 (6)
$C_1^{\varepsilon1}$	0.3939 (2)	0.7659 (1)	0.3906 (1)	0.0516 (8)
C_1^ζ	0.3792 (2)	0.7957 (1)	0.4279 (1)	0.0559 (8)
$C_1^{\varepsilon2}$	0.4481 (3)	0.7912 (1)	0.4642 (1)	0.0556 (8)
$C_1^{\delta2}$	0.5318 (2)	0.7576 (1)	0.46378 (9)	0.0435 (7)
C1′	0.7254 (2)	0.6064 (1)	0.39921 (7)	0.0276 (5)
O1	0.7894 (1)	0.58958 (8)	0.42800 (5)	0.0420 (4)
N2	0.7388 (1)	0.60826 (9)	0.35683 (6)	0.0276 (4)
C_2^α	0.8322 (2)	0.5965 (1)	0.34121 (7)	0.0276 (5)
C_2^β	0.8153 (2)	0.5740 (1)	0.29396 (8)	0.0318 (5)
C_2^γ	0.7579 (2)	0.5165 (1)	0.28894 (8)	0.0367 (6)
$C_2^{\delta1}$	0.7271 (2)	0.5028 (1)	0.24074 (9)	0.0464 (7)
$C_2^{\delta2}$	0.8168 (3)	0.4662 (1)	0.3115 (1)	0.0594 (9)
C2′	0.8957 (2)	0.6514 (1)	0.34706 (8)	0.0311 (5)
O2	0.8763 (1)	0.69383 (8)	0.36693 (7)	0.0506 (5)
O21	0.9772 (1)	0.64579 (8)	0.32792 (5)	0.0354 (4)
C21	1.0432 (2)	0.6958 (1)	0.33193 (9)	0.0439 (7)
C22	1.1120 (1)	0.69224 (8)	0.29753 (5)	0.0302 (5)
C23	1.1133 (1)	0.64485 (8)	0.26912 (5)	0.0368 (6)
C24	1.1781 (2)	0.6447 (1)	0.23784 (8)	0.0365 (6)
C25	1.2414 (2)	0.6912 (1)	0.23477 (8)	0.0352 (6)
C26	1.2406 (2)	0.7379 (1)	0.26317 (8)	0.0367 (6)
C27	1.1756 (2)	0.7384 (1)	0.29421 (8)	0.0338 (6)
(7)				
C1	0.4869 (2)	0.1530 (1)	0.39284 (9)	0.0462 (7)
C2	0.4943 (2)	0.1572 (2)	0.3441 (1)	0.0616 (9)
C3	0.5490 (2)	0.1028 (2)	0.4135 (1)	0.0622 (9)
C4	0.5119 (3)	0.2108 (2)	0.4153 (1)	0.068 (1)
O	0.3818 (1)	0.13945 (8)	0.39337 (5)	0.0383 (4)
C5	0.3438 (2)	0.1334 (1)	0.43164 (7)	0.0339 (6)
O_0	0.3907 (1)	0.13643 (9)	0.46792 (5)	0.0446 (5)
N1	0.2472 (2)	0.12307 (9)	0.42371 (6)	0.0344 (5)
C_1^α	0.1857 (2)	0.1176 (1)	0.45876 (7)	0.0305 (5)
C_1^β	0.1018 (1)	0.16235 (6)	0.45345 (5)	0.0337 (6)
C_1^γ	0.1377 (1)	0.22531 (6)	0.45751 (5)	0.0329 (6)
$C_1^{\delta1}$	0.1541 (1)	0.25209 (6)	0.49848 (5)	0.0377 (6)
$C_1^{\varepsilon1}$	0.1891 (2)	0.3094 (1)	0.5015 (1)	0.0497 (8)
C_1^ζ	0.2069 (2)	0.3400 (1)	0.4646 (1)	0.0555 (8)
$C_1^{\varepsilon2}$	0.1906 (3)	0.3133 (1)	0.4246 (1)	0.0646 (9)
$C_1^{\delta2}$	0.1561 (2)	0.2559 (1)	0.42113 (9)	0.0529 (8)
C1′	0.1422 (2)	0.0562 (1)	0.45840 (7)	0.0317 (5)
O1	0.0950 (2)	0.03662 (8)	0.42480 (6)	0.0514 (5)
N2	0.1533 (2)	0.02607 (9)	0.49556 (6)	0.0328 (5)
C_2^α	0.1055 (2)	−0.0311 (1)	0.49778 (8)	0.0349 (6)
C_2^β	0.1330 (2)	−0.0594 (1)	0.54276 (9)	0.0448 (7)
C_2^γ	0.0831 (2)	−0.1197 (1)	0.5481 (1)	0.0493 (7)
$C_2^{\delta1}$	0.0982 (3)	−0.1378 (1)	0.5960 (1)	0.0609 (9)
$C_2^{\delta2}$	0.1235 (3)	−0.1656 (2)	0.5191 (1)	0.078 (1)
C2′	−0.0047 (2)	−0.0261 (1)	0.48738 (9)	0.0445 (7)
O2	−0.0570 (2)	−0.0577 (1)	0.46361 (8)	0.0681 (7)
O21	−0.0392 (1)	0.01588 (9)	0.51051 (6)	0.0507 (5)
C21	−0.1423 (2)	0.0267 (1)	0.5077 (1)	0.0546 (8)
C22	−0.1589 (1)	0.08786 (8)	0.52278 (6)	0.0423 (6)
C23	−0.0807 (1)	0.12499 (8)	0.53663 (6)	0.0410 (6)
C24	−0.0995 (2)	0.1817 (1)	0.54853 (9)	0.0457 (7)
C25	−0.1945 (2)	0.2022 (1)	0.5469 (1)	0.0498 (7)
C26	−0.2721 (2)	0.1650 (1)	0.5336 (1)	0.0518 (8)
C27	−0.2544 (2)	0.1085 (1)	0.5212 (1)	0.0487 (7)

were obtained in 1654 attempts starting from random phases. The final correlation coefficient (Fujinaga & Read, 1987) was 88.7% (very convincing), and the solution consisted of 234 of the 238 atoms, so it was suitable for immediate refinement. The refinement was performed with full-matrix without blocking using *SHELXL*97 (Sheldrick, 1997*b*; Sheldrick & Schneider, 1997) and the scattering factors provided by the program. The H-atom coordinates were calculated geometrically and refined using the *SHELXL*97 riding model. For dipeptide synthesis L-amino acids were used as precursors (Clausen *et al.*, 1984). Thus, the enantiomers with the *S*-configuration at the chiral centres were selected and the signs of the torsional angles were in accordance with this assignment; the Flack parameter refined as −0.19 (Flack, 1983). The molecular geometry was calculated by the program *PLATON* (Spek, 1982) incorporated into the *EUCLID* (Spek, 1982) package. Drawings were prepared using *PLUTON* (Spek, 1982) and *ORTEPII* (Johnson, 1976). Final atomic coordinates and equivalent isotropic thermal parameters are listed in Table 2.† The calculations were performed on the Silicon Graphics workstation OCTANE of the Laboratory for Chemical Crystallography and Biocrystallography, Rudjer Bošković Institute, Zagreb, Croatia.

3. Results and discussion

3.1. *Molecular and crystal structure*

Molecular structures of the seven conformers (Fig. 1) found in the unit cell are presented as *ORTEP* drawings (Johnson, 1976). Bond lengths and angles are listed in Tables 3 and 4. The conformation is defined by the characteristic torsion angles (Table 5). The superposition of the seven conformers in the unit cell illustrates the conformational differences (Fig. 2). Their optimized conformers obtained by molecular mechanics (BIOSYM/MSI, 1995) are shown in Fig. 3. Crystal packing and hydrogen-bond geometry are shown in Fig. 4 and Table 6.

3.1.1. *Conformational analysis*. A single crystalline polymorph containing seven conformers was obtained; no solvent molecule has been incorporated and the same polymorph was obtained from various solvent systems. This structure documents the well established conformational flexibility of small peptides. Molecules (1)–(6) exhibit the folded backbone of the peptide chain [χ_2^1 in (−)-*synclinal* conformations, Table 5], whereas the backbone of (7) is in an extended form [χ_2^1 = 178.6 (2)°, Fig. 1, molecule (7)]. The terminal part of the dipeptide is protected by the OBzl group. Thus, the classical conformation angle ω_2 cannot be used; instead, the conformation is described by the angle $C_2^\alpha-C2'-O21-$

† Supplementary data for this paper are available from the IUCr electronic archives (Reference: KA0045). Services for accessing these data are described at the back of the journal.

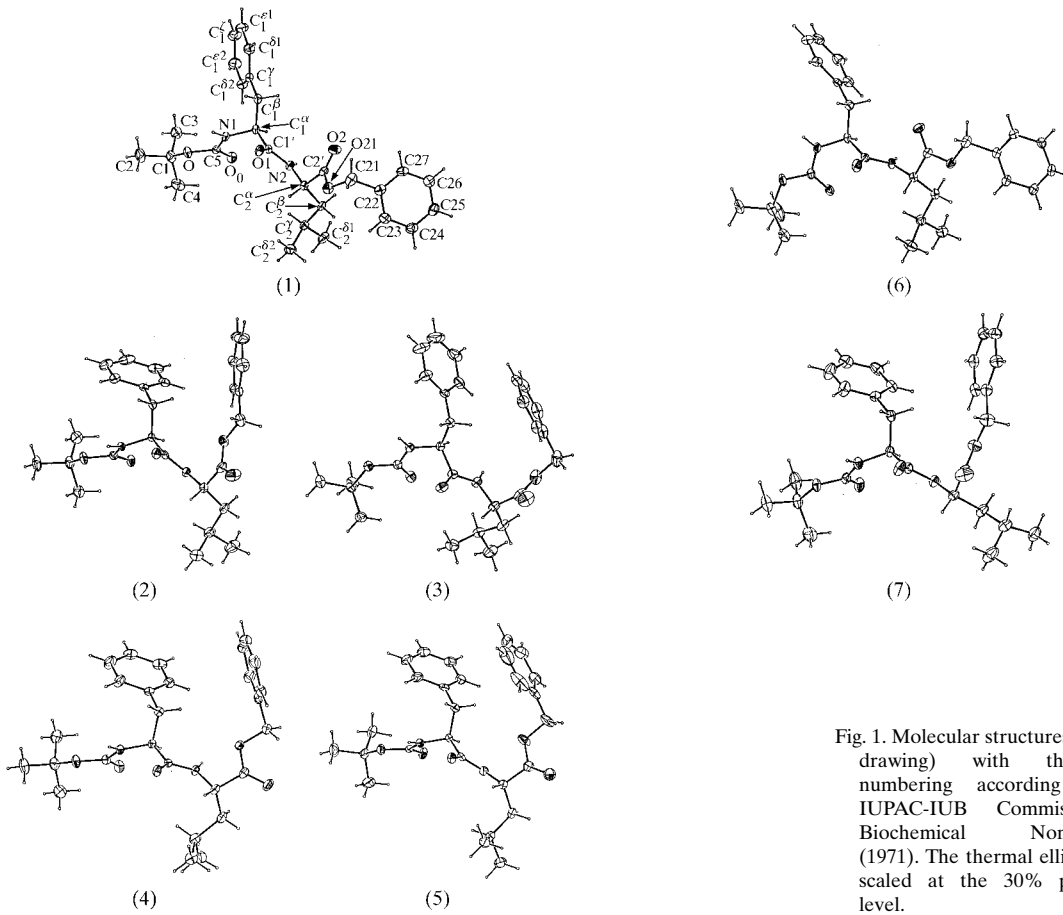


Fig. 1. Molecular structures (*ORTEP* drawing) with the atom numbering according to the IUPAC-IUB Commission on Biochemical Nomenclature (1971). The thermal ellipsoids are scaled at the 30% probability level.

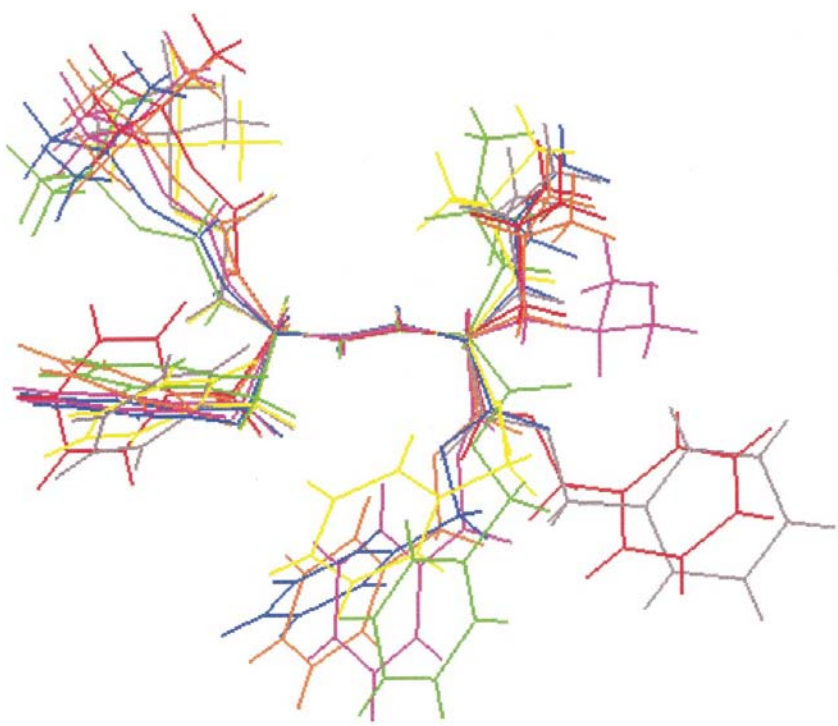


Fig. 2. Overlap diagram of seven conformers found in the crystal. Molecules: (1) red, (2) orange, (3) yellow, (4) green, (5) blue, (6) grey and (7) magenta.

Table 3. *Selected bond lengths (Å)*

Molecule	1	2	3	4	5	6	7
C1—C4	1.516 (3)	1.507 (4)	1.516 (3)	1.493 (3)	1.517 (3)	1.501 (4)	1.507 (4)
C1—C2	1.513 (4)	1.512 (4)	1.518 (3)	1.521 (4)	1.516 (4)	1.522 (4)	1.516 (4)
C1—C3	1.516 (4)	1.516 (4)	1.509 (4)	1.511 (4)	1.520 (4)	1.514 (4)	1.518 (4)
O—C1	1.466 (3)	1.477 (3)	1.473 (3)	1.477 (3)	1.470 (3)	1.465 (3)	1.476 (3)
O—C5	1.352 (3)	1.349 (3)	1.352 (3)	1.347 (3)	1.345 (3)	1.348 (3)	1.349 (3)
C5—O_0	1.217 (3)	1.216 (3)	1.220 (3)	1.219 (3)	1.213 (3)	1.219 (3)	1.216 (3)
N1—C5	1.339 (3)	1.339 (3)	1.343 (3)	1.345 (3)	1.357 (3)	1.332 (3)	1.338 (3)
N1—C_1^{α}	1.459 (3)	1.453 (3)	1.446 (3)	1.445 (3)	1.448 (3)	1.451 (2)	1.452 (3)
C_1^{α}—C_1^{β}	1.516 (3)	1.529 (3)	1.535 (3)	1.542 (3)	1.547 (3)	1.533 (3)	1.532 (3)
C_1^{β}—C_1^{γ}	1.531 (1)	1.516 (1)	1.512 (1)	1.513 (1)	1.522 (1)	1.519 (1)	1.518 (1)
C_1^{γ}—$C_1^{\delta 1}$	1.390 (1)	1.390 (1)	1.390 (1)	1.390 (1)	1.390 (1)	1.390 (1)	1.390 (1)
C_1^{γ}—$C_1^{\delta 2}$	1.374 (3)	1.377 (3)	1.375 (4)	1.375 (3)	1.374 (3)	1.384 (3)	1.366 (3)
$C_1^{\delta 1}$—$C_1^{\varepsilon 1}$	1.401 (4)	1.394 (3)	1.392 (4)	1.398 (3)	1.386 (3)	1.401 (3)	1.392 (3)
$C_1^{\varepsilon 1}$—C_1^{ζ}	1.373 (5)	1.375 (5)	1.362 (6)	1.369 (4)	1.373 (4)	1.367 (5)	1.376 (5)
C_1^{ζ}—$C_1^{\varepsilon 2}$	1.381 (4)	1.374 (4)	1.380 (7)	1.363 (4)	1.371 (4)	1.373 (5)	1.363 (4)
$C_1^{\varepsilon 2}$—$C_1^{\delta 2}$	1.383 (4)	1.377 (4)	1.378 (5)	1.390 (4)	1.384 (4)	1.382 (4)	1.391 (4)
C_1^{α}—C1′	1.532 (3)	1.525 (3)	1.521 (3)	1.515 (3)	1.520 (3)	1.513 (3)	1.520 (3)
O1—C1′	1.229 (3)	1.225 (3)	1.225 (3)	1.231 (3)	1.230 (3)	1.226 (3)	1.230 (3)
N2—C1′	1.337 (3)	1.328 (3)	1.337 (3)	1.327 (3)	1.338 (3)	1.336 (3)	1.323 (3)
N2—C_2^{α}	1.450 (3)	1.451 (3)	1.452 (3)	1.455 (3)	1.452 (3)	1.447 (3)	1.463 (3)
C_2^{α}—C_2^{β}	1.529 (3)	1.525 (3)	1.539 (4)	1.520 (4)	1.523 (3)	1.527 (3)	1.528 (3)
C_2^{β}—C_2^{γ}	1.529 (3)	1.522 (4)	1.524 (4)	1.536 (4)	1.525 (4)	1.527 (3)	1.554 (4)
C_2^{γ}—$C_2^{\delta 1}$	1.530 (3)	1.525 (4)	1.525 (4)	1.525 (4)	1.527 (4)	1.518 (4)	1.514 (4)
C_2^{γ}—$C_2^{\delta 2}$	1.527 (4)	1.517 (5)	1.523 (4)	1.512 (4)	1.526 (4)	1.518 (4)	1.523 (5)
C_2^{α}—C2′	1.519 (3)	1.514 (4)	1.517 (4)	1.521 (4)	1.522 (4)	1.523 (3)	1.508 (4)
O2—C2′	1.186 (3)	1.201 (3)	1.196 (3)	1.203 (3)	1.192 (3)	1.191 (3)	1.198 (3)
O21—C2′	1.337 (3)	1.325 (3)	1.343 (4)	1.326 (3)	1.328 (3)	1.332 (3)	1.314 (3)
O21—C21	1.466 (3)	1.443 (3)	1.455 (4)	1.461 (3)	1.464 (3)	1.451 (3)	1.427 (3)
C21—C22	1.497 (4)	1.502 (4)	1.498 (4)	1.520 (3)	1.483 (5)	1.503 (3)	1.497 (4)
C22—C23	1.391 (4)	1.390 (1)	1.390 (1)	1.390 (1)	1.390 (1)	1.390 (1)	1.390 (1)
C23—C24	1.378 (4)	1.386 (4)	1.399 (5)	1.399 (3)	1.363 (8)	1.386 (3)	1.377 (3)
C24—C25	1.374 (4)	1.366 (5)	1.354 (5)	1.380 (5)	1.373 (9)	1.381 (4)	1.378 (4)
C25—C26	1.373 (4)	1.386 (4)	1.369 (5)	1.371 (5)	1.339 (7)	1.377 (4)	1.383 (4)
C26—C27	1.381 (4)	1.381 (4)	1.380 (5)	1.383 (4)	1.375 (5)	1.382 (4)	1.373 (4)
C27—C22	1.381 (4)	1.381 (3)	1.367 (4)	1.385 (3)	1.353 (4)	1.377 (3)	1.387 (3)

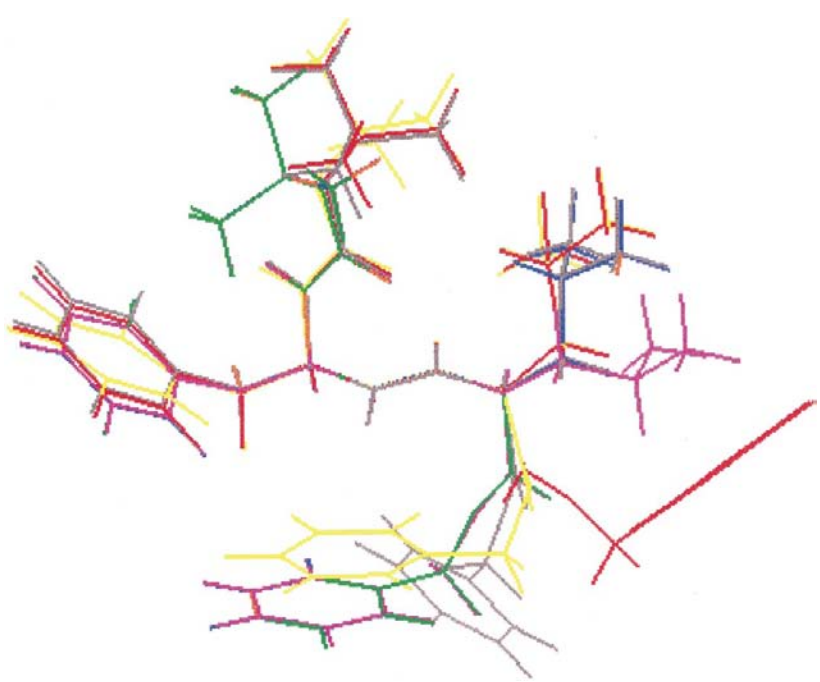


Fig. 3. Overlap diagrams of optimized conformers using molecular mechanics. The selection of colours is the same as in Fig. 2.

Table 4. *Selected bond angles (°)*

Molecule	1	2	3	4	5	6	7
O—C1—C4	110.7 (2)	109.5 (2)	102.1 (2)	108.2 (2)	110.2 (2)	110.7 (2)	110.1 (3)
O—C1—C2	102.4 (2)	110.8 (2)	111.3 (2)	101.9 (2)	101.6 (2)	102.2 (2)	102.1 (2)
O—C1—C3	109.5 (2)	102.1 (2)	109.3 (2)	111.8 (2)	110.5 (2)	110.4 (2)	109.6 (2)
C2—C1—C4	111.5 (2)	113.4 (2)	110.2 (2)	111.1 (3)	111.1 (2)	111.6 (3)	111.0 (3)
C3—C1—C2	109.8 (2)	109.8 (2)	112.5 (2)	110.2 (3)	111.2 (2)	110.4 (3)	110.9 (3)
C3—C1—C4	112.5 (2)	110.7 (3)	111.0 (2)	113.1 (3)	111.7 (2)	111.3 (3)	112.7 (3)
C1—O—C5	120.7 (2)	119.6 (2)	120.3 (2)	120.9 (2)	120.0 (2)	120.2 (2)	120.9 (2)
O—C5—O_0	125.3 (2)	125.0 (2)	124.5 (2)	125.6 (2)	125.4 (2)	125.0 (2)	125.0 (2)
O—C5—N1	109.4 (2)	110.1 (2)	111.2 (2)	109.7 (2)	109.8 (2)	111.4 (2)	109.9 (2)
N1—C5—O_0	125.3 (2)	124.9 (2)	124.3 (2)	124.7 (2)	124.8 (2)	123.6 (2)	125.0 (2)
C5—N1—C_1^α	122.3 (2)	120.4 (2)	118.3 (2)	121.1 (2)	119.9 (2)	118.8 (2)	122.2 (2)
N1—C_1^α—C1′	108.6 (2)	110.8 (2)	111.2 (2)	111.7 (2)	111.1 (2)	112.3 (2)	109.7 (2)
N1—C_1^α—C_1^β	110.1 (2)	110.8 (2)	110.9 (2)	112.1 (2)	111.0 (2)	110.5 (2)	111.2 (2)
C_1^α—C_1^β—C_1^γ	115.6 (1)	108.8 (1)	113.8 (1)	112.3 (1)	111.6 (1)	114.0 (1)	113.0 (1)
C_1^β—C_1^γ—$C_1^{\delta 1}$	117.6 (1)	119.9 (1)	120.1 (1)	119.9 (1)	120.0 (1)	120.7 (1)	120.3 (1)
C_1^β—C_1^γ—$C_1^{\delta 2}$	123.1 (1)	120.7 (1)	120.6 (2)	121.1 (1)	120.8 (1)	119.8 (1)	120.5 (1)
C_1^β—C_1^α—C1′	111.4 (2)	111.2 (2)	107.5 (2)	109.2 (2)	108.4 (2)	108.3 (2)	108.9 (2)
O1—C1′—C_1^α	122.5 (2)	122.7 (2)	121.9 (2)	122.8 (2)	121.4 (2)	123.2 (2)	120.3 (2)
O1—C1′—N2	122.6 (2)	123.0 (2)	123.2 (2)	123.1 (2)	123.6 (2)	122.6 (2)	121.7 (2)
N2—C1′—C_1^α	114.9 (2)	114.3 (2)	114.8 (2)	114.1 (2)	114.9 (2)	114.1 (2)	118.0 (2)
C_2^α—N2—C1′	121.7 (2)	121.7 (2)	123.8 (2)	125.0 (2)	123.8 (2)	123.4 (2)	119.9 (2)
N2—C_2^α—C_2^β	109.4 (2)	109.8 (2)	111.2 (2)	109.6 (2)	112.4 (2)	109.9 (2)	110.9 (2)
C_2^α—C_2^β—C_2^γ	115.3 (2)	115.8 (2)	115.3 (2)	114.0 (2)	115.0 (2)	113.5 (2)	114.1 (2)
C_2^β—C_2^γ—$C_2^{\delta 1}$	109.9 (2)	109.6 (3)	114.6 (2)	110.0 (3)	111.6 (2)	110.6 (2)	109.5 (2)
C_2^β—C_2^γ—$C_2^{\delta 2}$	111.8 (2)	111.7 (3)	110.2 (2)	111.1 (3)	109.6 (2)	111.3 (2)	110.4 (3)
$C_2^{\delta 1}$—C_2^γ—$C_2^{\delta 2}$	110.5 (2)	110.3 (3)	111.6 (3)	111.5 (3)	110.1 (2)	110.9 (2)	111.5 (3)
C_2^β—C_2^α—C2′	109.1 (2)	109.2 (2)	112.0 (2)	111.1 (2)	110.3 (2)	113.8 (2)	110.5 (2)
N2—C_2^α—C2′	111.2 (2)	112.2 (2)	107.9 (2)	111.3 (2)	110.9 (2)	108.9 (2)	111.5 (2)
O2—C2′—C_2^α	125.5 (2)	123.0 (3)	125.4 (3)	122.9 (2)	124.1 (3)	124.6 (2)	126.3 (3)
O21—C2′—C_2^α	109.5 (2)	113.4 (2)	110.6 (2)	112.9 (2)	112.0 (2)	111.6 (2)	111.0 (2)
C2′—O21—C21	115.8 (2)	117.4 (2)	117.4 (2)	114.6 (2)	116.6 (2)	115.8 (2)	120.8 (2)
O2—C2′—O21	124.9 (2)	123.6 (3)	123.9 (3)	124.1 (2)	123.8 (3)	123.8 (2)	122.6 (3)
O21—C21—C22	110.7 (2)	108.3 (2)	110.7 (2)	109.5 (2)	104.8 (3)	109.7 (2)	109.2 (2)
C21—C22—C23	120.2 (3)	118.3 (1)	119.7 (2)	120.6 (1)	119.6 (2)	122.7 (1)	121.5 (1)
C21—C22—C27	121.2 (3)	122.0 (2)	120.7 (2)	119.9 (2)	121.2 (3)	118.0 (2)	119.0 (2)

Table 5. *Selected torsion angles (°)*

Molecule		1	2	3	4	5	6	7
Phe								
θ_0	C1—O—C5—N1	158.6 (2)	168.9 (2)	−168.6 (2)	163.5 (2)	175.7 (2)	−175.4 (2)	178.1 (2)
φ_1	C5—N1—C_1^α—C1′	−106.3 (2)	−122.3 (2)	−70.2 (3)	−118.2 (2)	−125.9 (2)	−70.3 (3)	−117.0 (2)
ψ_1	N1—C_1^α—C1′—N2	116.6 (2)	112.0 (2)	142.2 (2)	146.9 (2)	128.3 (2)	139.7 (2)	127.8 (2)
ω_0	C_1^α—N1—C5—O	−177.1 (2)	−169.3 (2)	173.4 (2)	−175.5 (2)	−172.5 (2)	−179.8 (2)	−176.8 (2)
χ_1^1	N1—C_1^α—C_1^β—C_1^γ	−67.5 (2)	−66.1 (2)	−69.4 (2)	−67.8 (2)	−60.1 (2)	−69.2 (2)	−64.2 (2)
χ_1^2	C_1^α—C_1^β—C_1^γ—$C_1^{\delta 1}$	175.8 (1)	−80.2 (1)	−68.1 (1)	85.0 (1)	−87.4 (1)	−54.4 (1)	−87.5 (1)
Leu								
$\varphi 2$	C1′—N2—C_2^α—C2′	−73.3 (3)	−64.6 (3)	−104.0 (3)	−120.2 (2)	−97.5 (3)	−81.2 (3)	−59.6 (3)
ψ_2	N2—C_2^α—C2′—O21	157.6 (2)	−16.7 (3)	−58.9 (3)	37.2 (3)	17.9 (3)	−171.6 (2)	−49.8 (3)
ω_1	C_2^α—N2—C1′—C_1^α	−179.4 (2)	171.7 (2)	172.6 (2)	−178.5 (2)	163.8 (2)	169.9 (2)	174.7 (2)
	C_2^α—C2′—O21—C21	168.8 (1)	179.3 (2)	164.9 (3)	−178.4 (1)	178.4 (2)	−179.6 (2)	−176.9 (2)
χ_2^1	N2—C_2^α—C_2^β—C_2^γ	−67.7 (3)	−64.4 (3)	−46.0 (3)	−69.1 (3)	−77.0 (3)	−61.7 (3)	178.6 (2)
χ_2^2	C_2^α—C_2^β—C_2^γ—$C_2^{\delta 1}$	162.5 (2)	166.3 (2)	−53.3 (3)	153.7 (3)	−65.1 (3)	169.3 (2)	−168.4 (3)

C21 (Table 5). Therefore, the global molecular conformation, folded or extended, is described with the torsion angle χ_2^1 towards the aliphatic moiety of Leu. In all conformers the Phe residue displays a single rotamer for $\chi_1^1 \simeq -60°$ (Table 5); according to data on the conformation of the Leu side-chains in linear oligopeptides (Cambridge Structural Database; Allen & Kennard, 1993), the g^- conformation for χ_2^1 is the most frequent whereas g^+ is less populated. However, two rotamers (for Phe) about χ_1^2 are found: *antiperiplanar* [in (1)] and (±)-*synclinal* [in (2)–(7)]. In the Leu residue the values of Ψ_2 (Table 5) span a variety of conformations. The superposition of the seven conformations in the crystal (Fig. 2) shows similarities in the vicinity of the planar

peptide bond. Thus, in the Phe fragment Φ_1 shows large variations from -70.1 (1) to -125.9 (2)°, whereas Ψ_1 values are clustered about 128 ± 20°; in the Leu residue Φ_2 shows no such large variations as Ψ_2 does (Table 5). The torsion angles Φ and Ψ of Phe and Leu are in the allowed regions of the Ramachandran diagram (Ramachandran *et al.*, 1963), except the values of Ψ_2 for the conformers (2) and (5) (Table 5) which are in low-populated regions of the Ramachandran diagram (Voet & Voet, 1990). The conformation of the Boc group defined by torsion angles Θ_0 and ω_0 (Table 5) is *trans–trans*, as observed in Boc–Phe–D–Leu–OMe (Doi *et al.*, 1993) and in other Boc-protected peptides (Benedetti *et al.*, 1980; Subramanian & Sahayamary, 1993). The overall molecular conformations of the molecules (1)–(6) are balanced in such a way that pronounced hydrophobic regions are well separated; the phenyl ring of Phe and the alkyl part of Leu are disposed on the opposite side of a peptide backbone (Fig. 1).

To examine the conformational flexibility of the title dipeptide in an undisturbed environment (*in vacuo*), molecular mechanics and molecular dynamics simulations (*DISCOVER*, Amber force field; BIOSYM/MSI, 1995) were used. All conformers found in the crystal were subjected to an optimization procedure using molecular mechanics. As expected, the optimization procedure (Fig. 3) ended with molecules that did not exhibit such a large variety of conformations as was found in the crystal (Fig. 2). Molecules (1)–(6) remain in a folded shape, whereas (7) keeps an extended conformation. All molecules are characterized by the same orientation of phenyl rings of the Phe residue. Optimized molecules (1)–(6) reveal more or less similar rotamers about χ_2^1. Significantly different orientation of the OBzl group in (1) before and after the optimization was an exception (Figs. 2 and 3). The conformational search using simultaneous rotation of 15° about φ_1, ψ_1 and φ_2, ψ_2 produced the lowest energy conformers characterized by the torsion angles $\varphi_1 \simeq -75°$, $\psi_1 \simeq 60°$ and $\varphi_2 \simeq -75°$, $\psi_2 \simeq -60°$ in the Phe and in the Leu residues, respectively. In the crystal these conformers were not detected. However, in the two-dimensional φ, ψ energy diagrams (for both residues), wide regions of 15–30 kJ mol^{-1} higher energy than the lowest value include all conformers found in the solid state. Optimized molecule (2) was subjected to molecular dynamics simulations performed at elevated temperatures (300–600 K) over 600 ps. The calculations reproduce the conformations observed in the crystal (Table 5). The largest flexibilities were about χ_1^2 (free rotation of the phenyl ring of Phe) and Ψ_2 (flexibility about the bond next to the OBzl group).

Thus, the expectation of less flexibility in the dipeptide conformation through end-protection is unfounded. It is interesting to see if and how protection affects the overall conformation of this particular

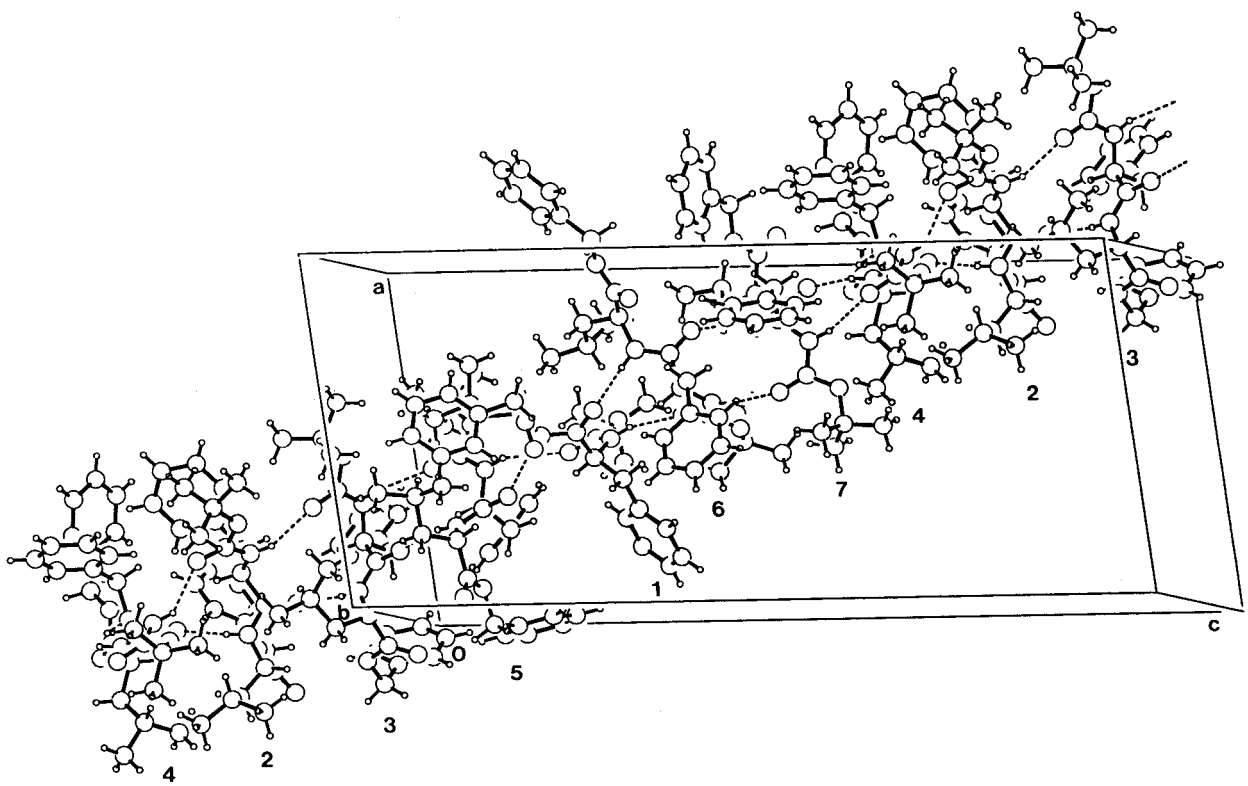
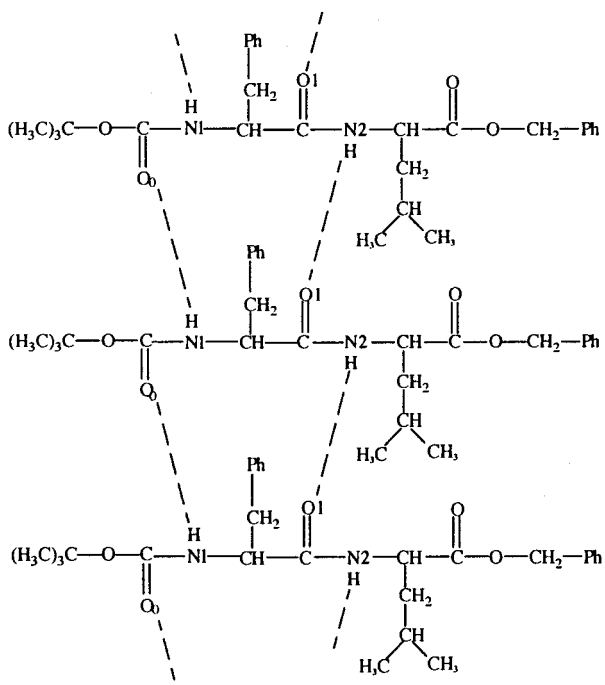


Fig. 4. Crystal packing with infinite sheets composed of molecules interconnected by N—H···O hydrogen bonds.

sequence. The Cambridge Structural Database (Allen & Kennard, 1993; version 5.15, April 1998 update) revealed 28 peptides with the specified sequence. Nine of them are the fragments of cyclic peptides and thus inappropriate for this analysis. In the remainder, 14 structures have no protected termini, whereas five do. There is no clearly distinguishable conformational feature that can be attributed to the influence of the protecting groups; besides, a set of five structures cannot be considered a statistically representative sample. However, one can generally observe that, in protected dipeptides with the Phe–Leu sequence, folded conformations are more populated whereas unprotected dipeptides keep a more extended form. In the title dipeptide, with blocked termini, we observed a 6:1 conformational preference in favour of the folded form.

3.1.2. *Crystal packing and hydrogen bonds*. The seven crystallographically independent molecules are interconnected *via* N—H···O hydrogen bonds involving the peptide groups, forming an infinite sheet [see (I), Fig. 4, Table 6]. Thus, a basic repeating unit is a sheet with seven dipeptide chains which is similar to the β-parallel sheet. Connection between basic repeating units into an infinite motif is realized by hydrogen bonds of N2—H of Leu [molecule (4)] and O1 of Phe [molecule (7), Table 6, Fig. 4]. On both sides of the sheets there are hydrophobic channels between phenyl rings of protecting benzyl groups and the Phe residues, and alkyl parts of Leu. The shortest intermolecular non-bonded distance of 3.74 Å occurs between benzyl groups [C23 (5)···C24 (6)] of two molecules related by a 2_1 operation.



(I)

Table 6. *Hydrogen bonds*

			D—H···A (Å)	H···A (Å)	D—H···A (°)
[4]†	$N2^{i}$—H···$O1^{i}$	[7]	2.773 (3)	1.92	162
[4]	$N1^{i}$—H···O_0^{ii}	[2]	2.962 (3)	2.23	141
[2]	$N2^{ii}$—H···$O1^{i}$	[4]	2.815 (2)	2.17	130
[2]	$N1^{ii}$—H···O_0^{iii}	[3]	2.942 (3)	2.13	154
[3]	$N2^{iii}$—H···$O1^{ii}$	[2]	2.803 (2)	1.93	171
[3]	$N1^{iii}$—H···O_0	[5]	2.968 (3)	2.19	147
[5]	N2—H···$O1^{iii}$	[3]	2.801 (3)	1.94	165
[5]	N1—H···O_0	[1]	3.253 (3)	2.52	141
[1]	N2—H···O1	[5]	2.867 (3)	2.02	163
[1]	N1—H···O_0^{iv}	[6]	2.894 (2)	2.05	161
[6]	$N2^{iv}$—H···O1	[1]	2.891 (3)	2.01	176
[6]	$N1^{iv}$—H···O_0^{iv}	[7]	2.923 (3)	2.06	166
[7]	$N2^{iv}$—H···$O1^{iv}$	[6]	2.785 (3)	1.97	153
[7]	$N1^{iv}$—H···O_0^{iv}	[4]	3.125 (3)	2.34	149

† Seven molecules [1]–[7] in the asymmetric unit. Molecules obtained by symmetry operations are in accord with those in Fig. 4. Symmetry codes: (i) $-x, \frac{1}{2}+y, -z$; (ii) $1-x, \frac{1}{2}+y, -z$; (iii) $1-x, -\frac{1}{2}+y, -z$; (iv) $1-x, \frac{1}{2}+y, 1-z$.

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