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Crystal structure of Boc-Leu-ΔPhe-Ile-ΔPhe-Ile-OCH_3, $C_{42}H_{59}N_5O_8$

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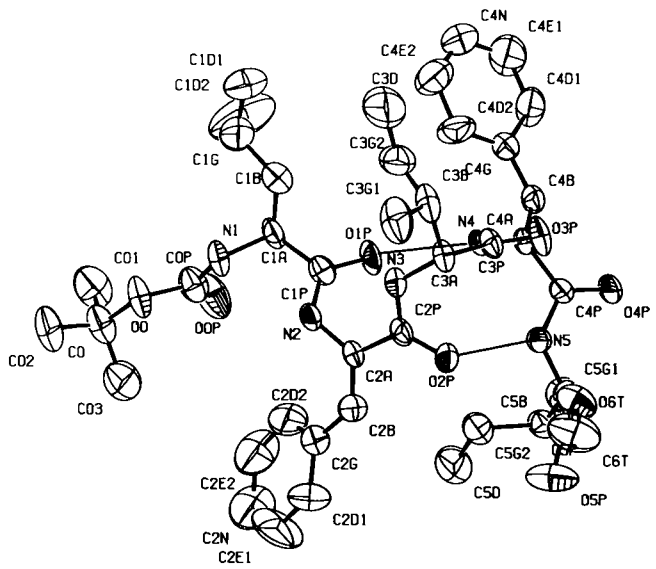

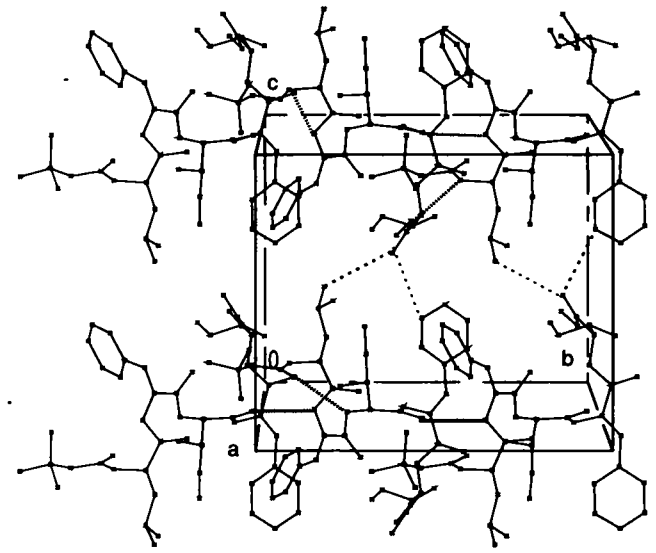

Abstract

$C_{42}H_{59}N_5O_8$, monoclinic, $P12_11$ (No. 4), a = 11.324(2) Å, b = 15.558(9) Å, c = 13.010(2) Å, β = 106.15(2)°, V = 2201.7 Å^3, Z = 2, $R_{gt}(F)$ = 0.072, $wR_{ref}(F^2)$ = 0.190, T = 293 K.

Source of material

The title peptide has been synthesised using the mixed anhydride coupling and the azalactone method according to [1] and [2], respectively. The peptide was crystallised from its solution in acetone-water mixture (4:1) by slow evaporation method.

Discussion

The systematic investigations on synthesis and design of peptides with α,β-dehydro-residues have lead to the development of a number of design rules. In these rules, α,β-dehydro-phenylalanine (ΔPhe) has been used most extensively [3]. It has been shown that the substitution of a ΔPhe at alternate sites induces a 3_{10}-helical conformation [4-7]. All these structures reported so far contained non-branched β-carbon residues [3]. However, in short peptides the conformations were found to be significantly distorted with branched β-carbon residues such as valine and isoleucine when compared with the similar sequences containing non-branched β-carbon residues [8-12]. Therefore, in order to standardize the formation of a 3_{10}-helical conformation and to estimate the extent of distortion in it due to the presence of branched β-carbon residues, a pentapeptide with two ΔPhe residues at positions 2 and 4 and Ile at positions 3 and 5 was synthesized. It may be mentioned here that this is the first structure with two branched β-carbon residue in a single peptide (upper figure). The crystal structure determination shows that a pentapeptide with two ΔPhe residues at alternate positions even in the presence of two branched β-carbon residues adopts a 3_{10}-helical conformation as in other sequences containing non-branched β-carbon residues [3]. The torsion angles of the backbone and the intramolecular hydrogen bonding scheme (upper figure) clearly show that it forms two consecutive type III β-turn conformations leading to an incipient 3_{10}-helical structure. However, due to the substitutions of Ile at positions 3 and 5, the torsion angles ω_3 = −168.3(5)° and ω_4 = 169.7(5)° are significantly distorted from the planarity in the peptide bonds of residues 3 and 4, and residues 4 and 5 respectively. The side chain torsion angles of ΔPhe2 and ΔPhe4 are χ_2^1 = 11.1(10)°, $\chi_2^{2,1}$ = −160.4(8)°, $\chi_2^{2,2}$ = 26.2(12)° and χ_4^1 = 4.2(10)°, $\chi_4^{2,1}$ = 166.9(8)°, $\chi_4^{2,2}$ = −8.9(12)°, respectively, indicating that the side chains of ΔPhe2 deviated from planarity. The side chain torsion angles of Ile3 and Ile5 of $\chi_3^{1,1}$ = 73.7(7)° and $\chi_3^{1,2}$ = −54.8(7)° and $\chi_3^{2,2}$ = −177.0(8)°, and $\chi_5^{1,1}$ = 72.6(7)°, $\chi_5^{1,2}$ = −52.4(7)° and $\chi_5^{2,1}$ = −172.6(7)°, respectively show that the side chains of both Ile3 and Ile5 adopt similar conformations. It is noteworthy that the present conformation of isoleucine was less frequently observed and perhaps less favourable of the two observed conformations for the side chain of isoleucine [13]. The deviation from planarity of the side chains of both ΔPhe residues and observation of the less favourable conformation for both residues of isoleucine are indicative of adverse effect on the preferred conformations of both ΔPhe and Ile residues. Overall, the presence of two ΔPhe residues at alternate positions results in the formation of a 3_{10}-helix despite the presence of two branched β-carbon residues. Therefore, it can be stated that a peptide containing two ΔPhe residues at alternate positions induces a 3_{10}-helical conformation in all conditions [3].

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In the crystal structure, the molecules are linked as continuous layers running parallel to the [100] direction by means of four hydrogen bonds (lower figure). Each molecule acts as a four fold donor and a threefold acceptor with N1 and O3 contributing to interdigitating hydrogen bonds. The two adjacent layers are not interwoven; they are however, linked by strong van der Waals forces and C–H···O hydrogen bonds, thus forming a three-dimensional continuum. Further examination of the structure with PLATON [14] showed that there were no solvent accessible voids in the crystal lattice.

Table 1. Data collection and handling.

Crystal:	colourless prism, size 0.1 × 0.2 × 0.3 mm
Wavelength:	Cu K_α radiation (1.54180 Å)
μ:	6.46 cm^{-1}
Diffractometer, scan mode:	Enraf Nonius CAD4, $\omega/2\theta$
$2\theta_{max}$:	150.66°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	4374, 4374
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 2717
$N(param)_{refined}$:	497
Programs:	PLATON [14], SHELXS-97 [15], SHELXL-97 [16]

Table 2. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	x	y	z	U_{iso}
H(01A)	2a	–0.0543	–0.0589	0.1770	0.08
H(01B)	2a	–0.1601	–0.0883	0.0775	0.08
H(01C)	2a	–0.1070	0.0052	0.0823	0.08
H(02A)	2a	0.0700	–0.1778	0.1586	0.08
H(02B)	2a	0.1113	–0.1914	0.0544	0.08
H(02C)	2a	–0.0238	–0.2130	0.0547	0.08
H(03A)	2a	0.0243	–0.0977	–0.1018	0.08
H(03B)	2a	–0.0578	–0.0189	–0.0912	0.08
H(03C)	2a	–0.1109	–0.1124	–0.0967	0.08
H(1)	2a	0.2928	0.0445	0.1490	0.08
H(1A)	2a	0.1802	0.2017	0.1316	0.08
H(1BA)	2a	0.4229	0.1639	0.2478	0.08
H(1BB)	2a	0.3634	0.2548	0.2452	0.08
H(1G)	2a	0.2928	0.1084	0.3349	0.08
H(1DA)	2a	0.4790	0.1584	0.4347	0.08
H(1DB)	2a	0.3811	0.1658	0.4990	0.08
H(1DC)	2a	0.4206	0.2479	0.4469	0.08
H(1DD)	2a	0.1708	0.1869	0.4039	0.08
H(1DE)	2a	0.1281	0.1883	0.2785	0.08
H(1DF)	2a	0.1966	0.2679	0.3418	0.08
H(2)	2a	0.3438	0.1034	–0.0077	0.08
H(2DA)	2a	0.2975	0.0719	–0.3774	0.08
H(2DB)	2a	0.1401	0.1344	–0.1531	0.08
H(2EA)	2a	0.1229	–0.0016	–0.4630	0.08
H(2EB)	2a	–0.0356	0.0630	–0.2445	0.08
H(2N)	2a	–0.0424	–0.0057	–0.4017	0.08
H(3)	2a	0.5516	0.2212	0.0720	0.08
H(3A)	2a	0.7114	0.3156	0.0082	0.08
H(3B)	2a	0.7897	0.3653	0.1855	0.08
H(3GA)	2a	0.8714	0.2430	0.1244	0.08
H(3GB)	2a	0.7833	0.1841	0.1674	0.08
H(3GC)	2a	0.8870	0.2366	0.2477	0.08
H(3GD)	2a	0.6163	0.3609	0.2432	0.08
H(3GE)	2a	0.6148	0.2605	0.2377	0.08
H(3DA)	2a	0.6877	0.3050	0.4105	0.08
H(3DB)	2a	0.7937	0.3561	0.3821	0.08
H(3DC)	2a	0.7915	0.2554	0.3767	0.08
H(4)	2a	0.4380	0.3802	0.0369	0.08
H(4DA)	2a	0.2969	0.6656	0.1521	0.08
H(4EA)	2a	0.2707	0.6648	0.3183	0.08
H(4N)	2a	0.3377	0.5495	0.4297	0.08
H(4EB)	2a	0.4065	0.4298	0.3616	0.08
H(4DB)	2a	0.4194	0.4280	0.1902	0.08
H(5)	2a	0.4362	0.4124	–0.1694	0.08
H(5A)	2a	0.4039	0.5372	–0.3193	0.08
H(6TA)	2a	0.7735	0.4098	–0.2779	0.08
H(6TB)	2a	0.6943	0.4182	–0.3973	0.08
H(6TC)	2a	0.6800	0.3372	–0.3300	0.08
H(5B)	2a	0.2575	0.4528	–0.4461	0.08
H(5GA)	2a	0.0922	0.5059	–0.3892	0.08
H(5GB)	2a	0.1959	0.5753	–0.3739	0.08
H(5GC)	2a	0.1811	0.5233	–0.2751	0.08
H(5DA)	2a	0.0892	0.2736	–0.3881	0.08
H(5DB)	2a	0.1055	0.3294	–0.4837	0.08
H(5DC)	2a	0.0414	0.3687	–0.4020	0.08
H(4B)	2a	0.3305	0.6001	0.0047	0.08
H(2B)	2a	0.3932	0.1804	–0.2472	0.08
H(5GD)	2a	0.2917	0.3217	–0.3483	0.08
H(5GE)	2a	0.2277	0.3610	–0.2667	0.08

Table 3. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(0)	2a	0.0059(6)	–0.0842(5)	0.0475(7)	0.060(4)	0.045(4)	0.103(6)	–0.011(3)	0.029(4)	–0.008(4)
C(01)	2a	–0.0872(7)	–0.0538(6)	0.1008(8)	0.075(5)	0.088(7)	0.131(7)	–0.015(5)	0.053(5)	–0.027(6)
C(02)	2a	0.0443(8)	–0.1748(5)	0.0819(8)	0.080(5)	0.051(5)	0.136(8)	–0.020(4)	0.040(5)	–0.003(5)
C(03)	2a	–0.0386(8)	–0.0778(7)	–0.0711(7)	0.099(7)	0.091(7)	0.095(7)	–0.029(5)	0.015(5)	–0.007(5)
O(0)	2a	0.1194(4)	–0.0354(3)	0.0895(4)	0.058(3)	0.030(2)	0.109(4)	–0.011(2)	0.020(3)	0.007(2)
C(0P)	2a	0.1223(6)	0.0521(4)	0.0748(6)	0.047(3)	0.047(4)	0.086(5)	–0.003(3)	0.026(3)	–0.005(3)
O(0P)	2a	0.0366(5)	0.0930(3)	0.0266(5)	0.062(3)	0.049(3)	0.125(5)	0.008(2)	–0.005(3)	0.002(3)
N(1)	2a	0.2343(4)	0.0805(3)	0.1236(4)	0.044(2)	0.025(3)	0.081(4)	–0.006(2)	0.022(2)	0.003(2)
C(1A)	2a	0.2584(6)	0.1734(4)	0.1345(5)	0.065(4)	0.023(3)	0.067(4)	–0.008(3)	0.026(3)	–0.008(3)
C(1B)	2a	0.3462(7)	0.1936(5)	0.2425(5)	0.084(5)	0.050(4)	0.066(4)	–0.007(4)	0.020(4)	–0.009(3)
C(1G)	2a	0.305(1)	0.1708(6)	0.3383(7)	0.146(9)	0.073(6)	0.081(6)	–0.006(6)	0.061(6)	–0.007(5)
C(1D1)	2a	0.405(1)	0.1872(8)	0.4387(7)	0.21(1)	0.12(1)	0.058(5)	–0.020(9)	0.034(7)	–0.005(6)
C(1D2)	2a	0.191(1)	0.206(2)	0.3409(9)	0.18(1)	0.32(3)	0.108(9)	0.01(2)	0.078(9)	0.03(1)
C(1P)	2a	0.3050(5)	0.2120(4)	0.0470(4)	0.038(3)	0.031(4)	0.057(3)	0.004(2)	0.014(2)	–0.005(2)
O(1P)	2a	0.3080(4)	0.2906(2)	0.0377(3)	0.076(3)	0.017(2)	0.078(3)	0.002(2)	0.027(2)	0.004(2)
N(2)	2a	0.3451(4)	0.1579(3)	–0.0184(3)	0.052(3)	0.023(2)	0.045(3)	–0.002(2)	0.010(2)	0.001(2)
C(2A)	2a	0.3881(5)	0.1883(3)	–0.1021(4)	0.053(3)	0.020(3)	0.045(3)	–0.002(2)	0.015(2)	0.000(2)
C(2G)	2a	0.2406(7)	0.1121(4)	–0.2520(5)	0.076(4)	0.050(4)	0.053(4)	–0.012(3)	0.015(3)	–0.001(3)
C(2D1)	2a	0.232(1)	0.0705(7)	–0.3477(6)	0.134(8)	0.100(7)	0.050(4)	–0.018(6)	0.010(5)	–0.019(4)

Table 3. Continued.

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(2D2)	2a	0.1388(8)	0.1073(7)	–0.2172(6)	0.101(6)	0.112(8)	0.050(4)	–0.045(6)	–0.012(4)	–0.002(4)
C(2E1)	2a	0.125(1)	0.0269(8)	–0.400(1)	0.14(1)	0.12(1)	0.104(8)	–0.036(8)	–0.039(8)	–0.041(7)
C(2E2)	2a	0.0321(9)	0.0640(9)	–0.2717(8)	0.084(6)	0.19(1)	0.081(6)	–0.052(7)	–0.013(5)	0.026(7)
C(2N)	2a	0.028(1)	0.024(1)	–0.3640(9)	0.118(9)	0.20(1)	0.082(7)	–0.09(1)	–0.025(6)	0.010(8)
C(2P)	2a	0.4958(5)	0.2491(3)	–0.0766(4)	0.056(3)	0.021(3)	0.052(3)	0.003(2)	0.020(3)	–0.003(2)
O(2P)	2a	0.5160(4)	0.2953(3)	–0.1474(3)	0.070(3)	0.031(2)	0.052(2)	–0.002(2)	0.025(2)	0.005(2)
N(3)	2a	0.5635(4)	0.2560(3)	0.0245(4)	0.042(2)	0.027(2)	0.051(3)	–0.003(2)	0.011(2)	0.006(2)
C(3A)	2a	0.6576(5)	0.3221(3)	0.0551(5)	0.039(3)	0.028(3)	0.060(3)	–0.003(2)	0.010(2)	0.006(3)
C(3B)	2a	0.7389(6)	0.3133(4)	0.1704(6)	0.051(3)	0.036(4)	0.083(5)	–0.010(3)	–0.010(3)	0.014(3)
C(3G1)	2a	0.8287(7)	0.2370(5)	0.1782(7)	0.068(5)	0.055(5)	0.114(7)	0.009(4)	–0.007(4)	0.027(4)
C(3G2)	2a	0.6684(8)	0.3103(5)	0.2524(5)	0.103(6)	0.062(5)	0.053(4)	0.004(4)	0.003(4)	–0.005(4)
C(3D)	2a	0.742(1)	0.3064(9)	0.3653(8)	0.25(2)	0.12(1)	0.080(7)	–0.06(1)	–0.032(8)	0.006(7)
C(3P)	2a	0.6028(5)	0.4120(4)	0.0362(4)	0.044(3)	0.023(3)	0.054(3)	0.003(2)	0.007(2)	0.002(2)
O(3P)	2a	0.6695(4)	0.4734(2)	0.0285(4)	0.054(2)	0.021(2)	0.098(3)	–0.001(2)	0.021(2)	0.006(2)
N(4)	2a	0.4808(4)	0.4220(3)	0.0229(3)	0.056(3)	0.019(2)	0.041(2)	–0.002(2)	0.006(2)	0.001(2)
C(4A)	2a	0.4235(5)	0.5017(3)	–0.0145(4)	0.051(3)	0.019(3)	0.044(3)	0.006(2)	0.012(2)	0.002(2)
C(4G)	2a	0.3571(6)	0.5464(4)	0.1485(5)	0.073(4)	0.041(4)	0.053(3)	–0.007(3)	0.026(3)	–0.006(3)
C(4D1)	2a	0.3169(9)	0.6160(5)	0.1931(7)	0.181(9)	0.041(5)	0.116(7)	0.007(5)	0.113(7)	–0.002(4)
C(4E1)	2a	0.304(1)	0.6170(7)	0.2940(9)	0.26(2)	0.062(7)	0.141(9)	0.000(8)	0.14(1)	–0.015(7)
C(4N)	2a	0.341(1)	0.5484(7)	0.3591(7)	0.18(1)	0.092(8)	0.067(5)	–0.023(7)	0.060(6)	–0.010(5)
C(4E2)	2a	0.3828(9)	0.4781(7)	0.3188(7)	0.149(8)	0.084(7)	0.073(5)	0.017(6)	0.052(5)	0.014(5)
C(4D2)	2a	0.3905(8)	0.4773(6)	0.2157(6)	0.141(7)	0.068(5)	0.052(4)	0.029(5)	0.044(5)	0.000(4)
C(4P)	2a	0.4174(5)	0.5274(4)	–0.1250(4)	0.052(3)	0.030(3)	0.038(3)	–0.003(2)	0.009(2)	–0.004(2)
O(4P)	2a	0.4051(4)	0.6029(2)	–0.1563(3)	0.080(3)	0.020(2)	0.051(2)	0.004(2)	0.014(2)	0.003(2)
N(5)	2a	0.4192(5)	0.4635(3)	–0.1945(3)	0.089(4)	0.023(2)	0.037(2)	0.008(2)	0.012(2)	0.004(2)
C(5A)	2a	0.3944(6)	0.4756(4)	–0.3079(4)	0.082(4)	0.034(3)	0.035(3)	0.000(3)	0.014(3)	0.005(2)
C(5P)	2a	0.4879(7)	0.4304(4)	–0.3508(5)	0.082(5)	0.053(4)	0.041(3)	0.002(3)	0.012(3)	–0.006(3)
O(5P)	2a	0.4636(6)	0.3893(5)	–0.4324(4)	0.115(4)	0.128(5)	0.062(3)	0.021(4)	0.017(3)	–0.039(3)
O(6T)	2a	0.6009(5)	0.4410(3)	–0.2931(4)	0.089(4)	0.066(4)	0.089(4)	0.009(3)	0.024(3)	–0.022(3)
C(6T)	2a	0.6949(9)	0.3980(8)	–0.3274(9)	0.095(7)	0.127(9)	0.117(8)	0.016(7)	0.024(6)	–0.041(7)
C(5B)	2a	0.2627(6)	0.4523(4)	–0.3696(5)	0.077(4)	0.040(4)	0.048(3)	0.004(3)	0.009(3)	–0.003(3)
C(5G1)	2a	0.1748(7)	0.5205(6)	–0.3501(6)	0.079(5)	0.072(5)	0.076(5)	0.002(4)	0.014(4)	0.000(4)
C(5D)	2a	0.1048(9)	0.3304(7)	–0.4101(7)	0.112(7)	0.082(6)	0.088(6)	–0.024(5)	0.006(5)	–0.005(5)
C(4B)	2a	0.3686(5)	0.5520(4)	0.0421(4)	0.056(3)	0.026(3)	0.051(3)	0.002(2)	0.019(3)	0.002(2)
C(2B)	2a	0.3468(6)	0.1629(4)	–0.2022(5)	0.072(4)	0.045(4)	0.045(3)	0.001(3)	0.015(3)	0.000(3)
C(5G2)	2a	0.2286(7)	0.3615(5)	–0.3410(6)	0.086(5)	0.050(4)	0.060(4)	–0.010(4)	0.006(4)	–0.001(3)

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