SHORT PAPER

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Formation of a turn like structure in $BocNH(CH_2)_2CON(C_6H_{11})CONH(C_6H_{11})$: an X-ray diffraction study†

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β-Alanine is an amino acid which is important in the design of diverse peptides. Crystallographic study shows that the N-acyl adduct of β-Alanine, an ω-amino acid important in peptide design for the production of structural and functional diversities, and N,N′-dicyclohexyl urea(DCU) forms a turn like structure without any intra-molecular hydrogen bonding.

Keywords : β-Alanine, turn, *trans* peptide bond, N,N'-dicyclohexyl urea (DCU)

β-Alanine (β-Ala) occurs widely in the animal and plant kingdoms. Representative β-Ala containing natural peptides[1] include carnosine,[2] efrapeptin,[3] roseotoxin[4] and leucinostatin.[5] β-Alanine has a larger degree of conformational variability than the α-amino acids, leading to a greater diversity of backbone structures in peptides and polypeptides.

The design and the development of molecular tools that can force flexible amino acid residues to adopt energetically favorable conformations has attracted considerable attention.[6] Various reports of short linear- and homodetic cyclic-peptides show the frequent occurrence of two distinctly different conformational characteristics, *i.e.* the extended and the folded conformations, of the β-Ala residue.[7-9] The observation of novel helical folds in peptide oligomers of acyclic[10] and cyclic β-amino acids,[11,12] the characterisation of α-helical structures in peptides incorporating β-Ala–γAbu segments,[13] (γ Abu ≡ γ-amino isobutyric acid), and the demonstration of proteolytic stability of a model β-hexa peptide,[14] have provided a dramatic new impetus for the use of β-Ala in peptide and protein design. Very recently a report shows the formation of parallel β-sheet aggregation in crystals of a short synthetic peptide containing only non-coded amino acids such as β-Ala, and α-aminoisobutyric acid (Aib).[15]

In the present paper we wish to report the solid state conformational preference of the N-acyl adduct of Boc-β-Ala and N,N'-dicyclohexylurea (DCU), $BocNH(CH_2)_2CON(C_6H_{11})$-$CONH(C_6H_{11})$ in the solid state.

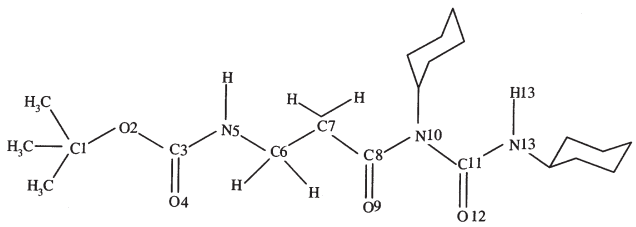

Fig. 1 The chemical structure of $BocNH(CH_2)_2CON(C_6H_{11})CONH(C_6H_{11})$.

It was anticipated that since the molecule has C3=O4 and N13–H13 groups separated by the required number of bonds to form a β-turn[16] like structure by intramolecular hydrogen bonding, the nearly *gauche* or *cis* conformation around the dihedral C6–C7–C8–N10 and C7–C8–N10–C11 may lead to a turn like structure. There are very few reports of turn formation in β-Ala containing dipeptides.[17]

The torsion angle C6–C7–C8–N10 is 124.58(0.27)°, C7–C8–N10–C11 is –1.50(0.34)° while the torsion angle C7–C8–N10–C20 is 175.01(0.22)°. There is a turn in the molecule at both C8 as well as N10, *i.e.* at the peptide bond.

There are two cyclohexane rings in the molecule, C20–C21–C22–C23–C24–C25 and C14–C15–C16–C17–C18–C19, both rings being in the chair form.

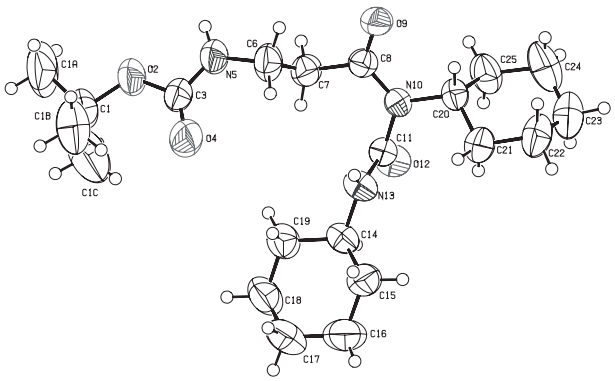

Fig. 2 An ORTEP representation of the molecular structures of $BocNH(CH_2)_2CON(C_6H_{11})CONH(C_6H_{11})$, in the solid state. The thermal ellipsoids are shown to the 50% probability level.

In the cyclohexane ring C20–C21–C22–C23–C24–C25, the atoms C20, C25, C23, C22 are coplanar with C21 deviating by –0.673(5)Å and C24 deviating by 0.637(8)Å while in the ring C14–C15–C16–C17–C18–C19 the atoms C14, C15, C17, C18 are coplanar with C16 deviating by –0.644(7)Å and C19 deviating by 0.667(6)Å.

The molecules are stacked by hydrophobic interactions along the *b* axis. There is intermolecular hydrogen bonding in the molecule between N5---O9 [–*x*+1, –*y*+1, –*z*+1] and N13---O12 [–*x*+1, *y*+1/2, –*z*+1/2] with donor acceptor distances of 2.894(4)Å and 2.855(3)Å respectively. So the hydrogen bonding results in the interconnection of three different molecules.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Cremer Pople puckering parameters[18] of the rings

Ring	Size	q_2 [Å]	ϕ_2 [°]	θ [°]	Type
C20–C21–C22–C23–C24–C25	6	0.0191 (0.0044)	–147.03 (11.69)	178.06 (0.46)	C
C14–C15–C16–C17–C18–C19	6	0.0158 (0.0050)	102.85 (14.48)	178.39 (0.51)	C

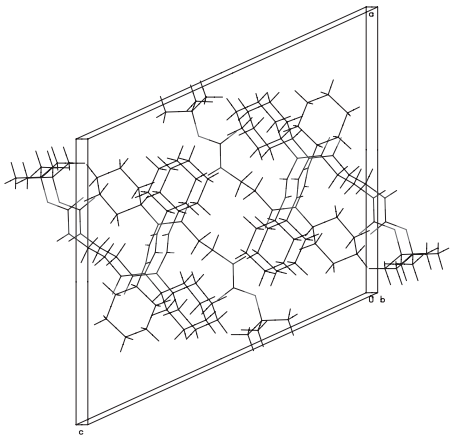

Fig. 3 A view of the packing of the molecules in the unit cell

Conclusion

The molecule shows a remarkable property of turn formation without any intramolecular hydrogen bonding. Due to steric reasons, the *trans* conformation of the peptide bond (C7–C8–N10–C20 = 175.01°) is preferentially stabilised. As a result the molecule has a turn like structure. Further structural modification may help to generate super secondary structure like β-hairpin.

Experimental

Synthesis: DCC 1.12 g (5.4 mmol) was added to a solution of Boc-β-Ala-OH (0.51 g (2.7 mmol)) in 15 ml CH_2Cl_2 (15 cm^3) The mixture was stirred for 2 days at room temperature. Then the residue was taken in ethylacetate (50 ml) and the DCU was filtered off. The organic layer was washed with 1M sodium carbonate (3 × 50 ml) and brine (2 × 50 ml), dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield solid material. The compound was purified by silica gel column chromatography using MeOH/$CHCl_3$ as eluent. The pure compound was crystallised from MeOH/H_2O.

Spectroscopic and microanalysis data: m.p.=129–130°C IR(KBr): 3329(N-H), 1626(CO), 1576(CO) cm^{-1} ^{1}H NMR(300MHz) in $CDCI_3$: δ 1.41(9H, s, -$C(CH_3)_3$), 1.09-1.30 (11H, m, cyclohexyl), 1.60–1.88(11H, m, cyclohexyl), 2.61(2H, t, β-AlaC^{α}-H), 3.43(2H, m, β-AlaC^{β}-H), 5.19(1H, br, β-Ala N-H), 7.20(1H, br, cyclohexyl-N-H) Calcd. For $C_{21}H_{37}N_3O_4$: C, 63.77; H, 9.43; N, 10.63 %. Found: C, 63.59; H, 9.25; N, 10.82 %.

Crystal data: $C_{21}H_{37}N_3O_4$, M_r = 395.54, monoclinic, *a* = 16.015(10)Å, *b*= 9.068(3)Å, *c* = 17.893(21)Å, β = 114.432(2)°, V = 2365.7(2)$Å^3$, *T* = 294K, space group $P2_1/c$, Z = 4, μ = 0.077mm^{-1}, 7459 reflections measured, 3973 unique reflections, R_{int} =0.031.

The experimental data were collected at room temperature using a Nonius-Kappa CCD diffractometer with Mo–Kα radiation (λ =0.7107 Å) and the φ–ω scan technique [$0 \le h \le 18$, $0 \le 0 \le 10$, $-20 \le l \le 18$].

The structure was solved by direct methods (SHELXS-97).[19] The non-hydrogen atoms were refined anisotropically using full-matrix least squares on F^2 (SHELXL-97).[19] The final *R*-value was 0.0624 for 3064 *Fo* > 4σ(Fo), wR2 = 0.1813, *S* = 1.066 using 386 parameters and no restraints. The weighting scheme, $w = 1 / [\sigma^2(F_o^2) + (0.0828 * P)^2 + 0.87 * P]$ where $P = (\text{Max} (F_o^2, 0) + 2 * F_c^2)/ 3$ gave satisfactory analysis of the variance. Full crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 199755.

Data collection: COLLECT[20], cell refinement: DENZO-SMN[21], data reduction: DENZO-SMN; molecular graphics: PLATON[22]

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