SHORT PAPER

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A folded conformation around the methylene group in simple Boc–NH–$(CH_2)_3$–NH–Boc: an X-ray diffraction study†

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Structural studies on model compounds Boc–NH–$(CH_2)_2$–NH–Boc (**1**) and Boc–NH–$(CH_2)_3$–NH–Boc (**2**) have shown the inherent tendency of the propylene group to adopt a folded conformation, which may help in peptide and peptide nucleic acid (PNA) design.

Keywords: folded conformation, dibasic acids, peptide nucleic acid

Various examples are known of the introduction of ω-amino acids having two functional groups separated by polymethylene units of varying lengths into polypeptides for the production of structural and functional diversities.[1–5] Dibasic acids of different lengths are used in the design of cyclopeptides to mimic β-turn and folded conformations.[6–8] In recent years several peptide designs have been reported where linear diacidic bases with varying polymethylene chain are being used to mimic β-sheet and cyclic structures.[8, 9] Interestingly, very recently ethylenediamine has been used to produce the helical strand in PNA.[10] Therefore, it is very important to know the inherent conformational preferences of these diacidic bases, in order to explore their potential use as a spacer linker in peptide design. Consequently, we have synthesised[11] two compounds **1** and **2**, where the central polymethylene units of the diacidic bases have no induced conformational effect from the neighbouring residues, and studied their solid-state structure by single crystal X-ray crystallography.[12]

Study of the crystal structures of the molecules shows that **1** lies on a centre of symmetry. However the two halves of **2** are not symmetric. The structure of **1** adopts an extended conformation ($\theta_2 = 180°$) comparable to that seen in case of Z–Pro–NH–$(CH_2)_2$–NH–Pro–Z [9] whereas the structure of **2** shows a folded conformation ($\theta_2 = –66.9°$). Nearly similar conformational preferences are observable in ω-amino acids like γ′-aminobutyric acid.[13–15]

The backbone torsion angles $\theta_1 = –86.4°$, $\theta_2 = –66.9°$, $\theta_3 = –176.5°$, $\theta_4 = 176.8°$ corresponding to *gauche* (-), *gauche* (-), *trans* and *trans* conformations respectively, characterise the folded structure of **2**. Significantly, the propylenediamine moiety in **2** inherently adopts the *gauche* conformation ($\theta_2 = –66.9°$). Hence propylenediamine can be used as a potential spacer linker to produce β-sheet like structures.

The intermolecular hydrogen-bonding pattern (Table 1) in the crystal lattice of **1** showed the formation of an infinite ribbon assembly, a similar assembly being visible in **2**. There are only two independent hydrogen bonds forming a 14-membered ring in **1** and a 16-membered ring in **2** that connect the molecules into ribbons.

From these structural studies we observe that propylenediamine has an inherent tendency to adopt a folded conformation which is necessary to mimic β–turn and to produce the helical conformation of the PNA strand. The structural flexibility of the methylene units of propylenediamine moiety in the PNA strand may help in nucleic acid recognition more effectively. Therefore propylenediamine is a potentially superior molecule than ethylenediamine in β–turn and PNA design.

Experimental

*Preparation of **1** and **2***: 2 ml of $^tBuOCON_3$ was added to 1 ml of ethylenediamine (or propylenediamine) with constant stirring at room temperature to get a white solid, **1**(or **2**). This product was then washed thoroughly with 4 (N) HCl, followed by washing with water. Prism shaped crystals of the pure product was obtained from a mixture of methanol-water. The compounds **1** and **2** possessed the following spectroscopic and micro analytical data.

Spectroscopic and micro analytical data: For Boc NH$(CH_2)_2$–NH Boc(1): M.p. =129–130°C. ^{1}H NMR (300.13 MHz) in $CDCl_3$: δ 1.43 (18H, s, –O–C$(CH_3)_3 \times 2$), 3.21 (4H, br, –CH_2–CH_2–), 4.87 (2H, br., –NH– × 2). ^{13}C NMR (75.47 MHz) in $CDCl_3$: δ 156.3 (C = O × 2), 79.3 (–C$(CH_3)_3 \times 2$), 40.8 (–CH_2– × 2), 28.3 (–$CH_3 \times 6$). Micro anal. calcd for **1** ($C_{12}H_{24}N_2O_4$) : C, 55.36; H, 9.29; N, 10.76. Found: C, 55.23; H, 9.15; N, 10.85.

For Boc NH$(CH_2)_3$–NH Boc(2): M.p. = 99–100°C. ^{1}H NMR (300.13 MHz) in $CDCl_3$: δ 1.37 (18H, s, –O–C$(CH_3)_3 \times 2$), 1.54 (2H,

Table 1 Intermolecular hydrogen bonds in **1** and **2**

Molecule	Donor (D)	Acceptor (A)	Distance (D—-A) Å	Symmetry relation
1	N5	O4	3.13(2)	*x*+1, *y*, *z*
2	N9	O4	2.97(1)	-*x*+1, -*y*, -*z*
2	N5	O11	2.90(2)	-*x*, -*y*+1, -*z*

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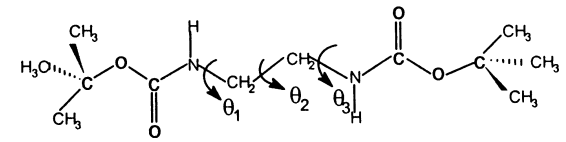
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



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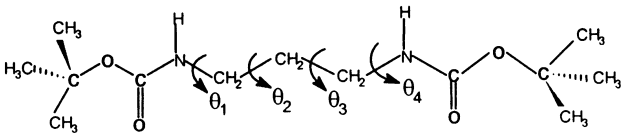

2

Fig. 1 The chemical structures of **1** and **2**.

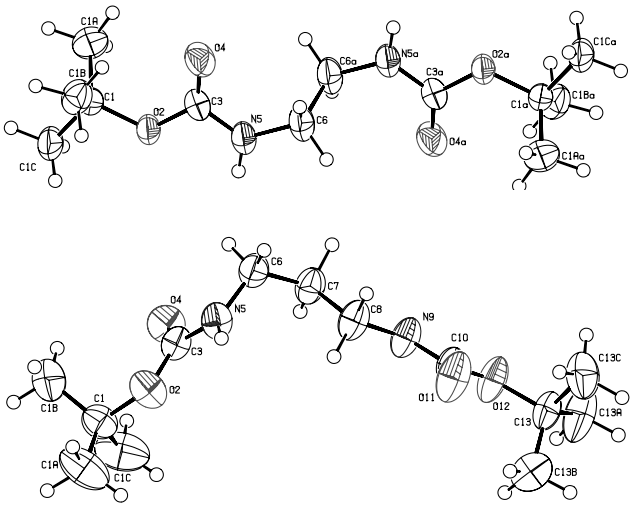

Fig. 2 An ORTEP representation of the molecular structures of **1** and **2**, in the solid state. The thermal ellipsoids are shown to the 50% probability level.

t, $-CH_2-CH_2-CH_2-$), 3.10 (4H, q, $CH_2-CH_2-CH_2-$), 5.05 (2H, br., –NH × 2). ^{13}C NMR (75.47 MHz) in $CDCl_3$: δ 156.1 (C=O × 2), 78.9 ($-C(CH_3)_3$ × 2), 37.5 ($-CH_2-$), 30.5 ($-CH_2-$ × 2), 28.3 ($-CH_3$ × 6). Micro anal. calcd for **2** ($C_{13}H_{26}N_2O_4$) : C, 56.91; H, 9.55; N, 10.21. Found : C, 56.70; H, 9.41; N, 10.32.

Crystal data for **1**(**2**): $C_{12}H_{24}N_2O_4$ ($C_{13}H_{26}N_2O_4$); Z = 2; P21/c (P-1); a = 5.238(2) (8.115(4)) Å; b = 8.823(4) (9.578(4)) Å; c = 16.187(8) (12.136(7)) Å; α = 90.00 (70.51(29))°; β = 95.80(30) (87.34(25))°; γ = 90.00 (68.38(29))°; M_r= 260.33(274.36); V= 744.20 (823.53) $Å^3$; μ = 0.09 (0.08) mm^{-1}, F (000) = 284(300).

X-ray data were collected at room temperature on a Nonius Kappa CCD single crystal diffractometer with Mo-Kα radiation (λ = 0.71070) and φ-ω scan. The structures were solved by direct methods with SHELXS-97 and refined by full-matrix least squares on F^2 using SHELXL-97.[14] All non-hydrogen atoms were refined anisotropically and hydrogens were located by refinement. The final cycle of refinement was based on 2144 unique reflections [I>2σ(I)] and 130 (276) variable parameters and converged to R_1 = 0.0479 (0.0517) and wR_2 = 0.1385 (0.1441). Full crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 175675 and CCDC175676.

Data collection: COLLECT (Nonius, 1997);[15] cell refinement: DENZO-SMN (Otwinowski & Minor, 1997);[16] data reduction: DENZO-SMN; molecular graphics: PLATON (Spek, 1999).[17]

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