

## Linear Oligopeptides. Part 147.<sup>1</sup> Chemical and Crystallographic Study of the Reaction between Benzyloxycarbonyl Chloride and $\alpha$ -Aminoisobutyric Acid

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From the reaction mixture of benzyloxycarbonyl chloride and  $\alpha$ -aminoisobutyric acid three crystalline compounds were isolated and characterized by chromatographic and spectroscopic techniques and X-ray diffraction. Two of them are polymorphic forms of the *N*-protected amino acid, which differ in the orientation of the phenyl ring relative to the urethane moiety and in the packing modes of the molecules, including the intermolecular hydrogen-bonding arrangements. The third compound is the *N*-protected dipeptide, the formation of which is not unexpected in the synthesis of the *N*-benzyloxycarbonyl amino acid derivative. The crystal structure of the symmetric carboxylic anhydride from the *N*-protected amino acid, a reasonable reactive intermediate in the formation of the *N*-protected dipeptide, is also described.

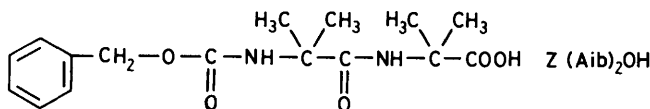
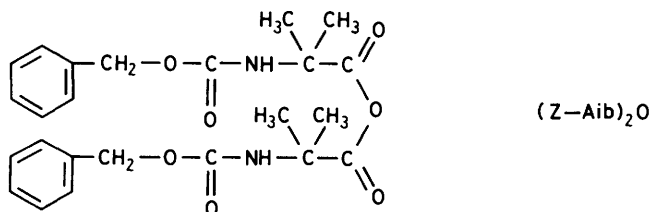
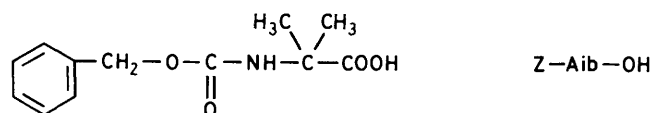
Our interest in a chemical and crystallographic study of the reaction between benzyloxycarbonyl chloride (Z-Cl) and  $\alpha$ -aminoisobutyric acid (H-Aib-OH) originated from the following considerations. (i) The expected product, Z-Aib-OH, has a melting range of either 72.5–74.5 or 88–89 °C.<sup>2,3</sup> According to McGahren and Goodman,<sup>3</sup> it is possible that the compound exhibits polymorphism, an unusual observation in amino acid derivatives. (ii) Preparation of *N*<sup>z</sup>-urethane-protected amino acids reveals the presence of small, but reproducible, amounts of contaminants which are identified as *N*<sup>z</sup>-urethane-protected homo-dipeptides and -tripeptides.<sup>4–13</sup> These findings have already been determined with benzyloxycarbonyl (Z), *t*-butyloxycarbonyl (Boc), fluoren-9-ylmethoxycarbonyl (Fmoc), and 2-biphenyl-4-ylisopropoxycarbonyl (Bpoc) derivatives. (iii) The well established high crystallinity of Aib derivatives<sup>14–16</sup> was expected to help us in identifying and characterizing the structure of the potential reactive intermediate(s) responsible for homodipeptide formation: these are the mixed carboxylic-carbonic anhydride (Z-Aib-OZ), and/or the symmetric carboxylic anhydride [(Z-Aib)<sub>2</sub>O], the *N*-carboxy-anhydride (Aib-NCA), and the oxazol-5(4*H*)-one from Z-Aib-OH.<sup>17–19</sup>

In this work we describe the results of the chemical study of the reaction between Z-Cl and H-Aib-OH and X-ray diffraction data on the crystal-state conformational preferences and intermolecular hydrogen-bonding arrangements of the  $\alpha$ - (lower melting point) and  $\beta$ - (higher melting point) forms of Z-Aib-OH, of the identified contaminant Z(Aib)<sub>2</sub>OH and the reactive intermediate symmetric carboxylic anhydride (Z-Aib)<sub>2</sub>O. The crystal structures of other *N*<sup>z</sup>-urethane-protected Aib derivatives (Boc-Aib-OH;<sup>14,20</sup> Fmoc-Aib-OH;<sup>21</sup> Adoc-Aib-OH,<sup>22</sup> where Adoc is 1-adamantylloxycarbonyl; and Boc-Aib-OPcp,<sup>1</sup> where OPcp is pentachlorophenoxy), Aib homodipeptides [Boc-(Aib)<sub>2</sub>OBzl,<sup>23</sup> where OBzl is benzyloxy], and Aib symmetric anhydride [(Pht-Aib)<sub>2</sub>O,<sup>1</sup> where Pht is phthaloyl] have already been reported.

### Experimental

**Materials.**—The synthesis and characterization of Z-Aib-OH ( $\alpha$ - and  $\beta$ -forms),<sup>2,3</sup> Z(Aib)<sub>2</sub>OH,<sup>2</sup> and (Z-Aib)<sub>2</sub>O<sup>3</sup> have already been described. We obtained the first three compounds by

fractional crystallization from an ethyl acetate–light petroleum solution of the crude, oily product isolated from the reaction mixture of Z-Cl and H-Aib-OH described by Leplawy *et al.*<sup>2</sup> The yields were 63% for the  $\alpha$ -form of Z-Aib-OH, 27% for the  $\beta$ -form of Z-Aib-OH, and 1.5% for Z(Aib)<sub>2</sub>OH. These compounds were characterized as follows: Z-Aib-OH ( $\alpha$ -form): m.p. 73–74 °C; t.l.c. (silica gel plates 60F-254, Merck)  $R_{F1}$  (chloroform–ethanol 9:1) 0.65,  $R_{F2}$  (butan-1-ol–acetic acid–water 3:1:1) 0.95,  $R_{F3}$  (ethanol) 0.75;  $\delta_H$  (200 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.59 (6 H, s,  $\beta$ -Me), 5.11 (2 H, s, benzylic CH<sub>2</sub>), 5.37 (1 H, s, urethane NH), and 7.35 (5 H, m, phenyl CH);  $\nu_{max}$  (KBr) 3 432 (weak) and 3 320 (strong) (NH), 1 719 (acid carbonyl), and 1 674 cm<sup>-1</sup> (urethane carbonyl) (Found: C, 60.9; H, 6.3; N, 6.0. Calc. for C<sub>12</sub>H<sub>15</sub>NO<sub>4</sub>: C, 60.75; H, 6.4; N, 5.95%); Z-Aib-OH ( $\beta$ -form): m.p. 84–85 °C;  $R_{F1}$  0.65,  $R_{F2}$  0.95,  $R_{F3}$  0.75;  $\delta_H$  (200 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.58 (6 H, s,  $\beta$ -Me), 5.11 (2 H, s, benzylic CH<sub>2</sub>), 5.37 (1 H, s, urethane NH), and 7.35 (5 H, m, phenyl CH);  $\nu_{max}$  (KBr) 3 432 (weak) and 3 330 (strong) (NH), 1 712 (acid



carbonyl), 1 701 and 1 686  $\text{cm}^{-1}$  (urethane carbonyl) (Found: C, 60.75; H, 6.4; N, 5.9); Z(Aib)<sub>2</sub>OH: m.p. 160–161 °C;  $R_F$ , 0.00,  $R_{F_2}$ , 0.90,  $R_{F_3}$ , 0.70;  $\delta_H$  (200 MHz;  $\text{CDCl}_3$ - $\text{Me}_2\text{SO}$  95:5;  $\text{Me}_4\text{Si}$ ) 1.53, 1.50 (12 H, 2 s,  $\beta$ -Me), 5.09 (2 H, s, benzylic  $\text{CH}_2$ ), 6.06 (1 H, s, urethane NH), 7.10 (1 H, s, peptide NH), and 7.34 (5 H, m, phenyl CH);  $\nu_{\text{max}}$  (KBr) 3 429 and 3 299 (NH), 1 721 (acid carbonyl), 1 703 (urethane carbonyl), 1 653  $\text{cm}^{-1}$  (peptide carbonyl) (Found: C, 59.4; H, 6.8; N, 8.6. Calc. for  $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5$ : C, 59.6; H, 6.9; N, 8.7%).

The symmetric anhydride (Z-Aib)<sub>2</sub>O was prepared by McGahren and Goodman either from Z-Aib-OH and thionyl chloride or by disproportionation of the mixed anhydride from Z-Aib-OH and pivaloyl chloride.<sup>3</sup> We obtained this compound in 45% yield by treatment of Z-Aib-OH with Z-Cl and triethylamine in anhydrous toluene: m.p. 100–101 °C;  $R_F$ , 0.85,  $R_{F_2}$  (toluene-ethanol 7:1) 0.60;  $\delta_H$  (200 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.45 (6 H, s,  $\beta$ -Me), 4.92 (1 H, s, urethane NH), 5.07 (2 H, s, benzylic  $\text{CH}_2$ ), and 7.36 (5 H, m, phenyl CH);  $\nu_{\text{max}}$  (KBr) 3 294 (NH), 1 814 and 1 742 (anhydride carbonyl), 1 699, 1 683, and 1 652 (weak)  $\text{cm}^{-1}$  (urethane carbonyl) (Found: C, 63.4; H, 6.3; N, 6.1. Calc. for  $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_7$ : C, 63.2; H, 6.2; N, 6.1%).

*Crystal Data for the  $\alpha$ -Form of Z-Aib-OH.*— $\text{C}_{12}\text{H}_{15}\text{NO}_4$ ,  $M = 237.2$ . Monoclinic,  $a = 11.708(3)$ ,  $b = 9.955(3)$ ,  $c = 10.866(3)$  Å,  $\beta = 103.5(3)^\circ$ ,  $V = 1\,231.5(1)$  Å<sup>3</sup>, space group  $P2_1/c$ ,  $Z = 4$ ,  $D_m = 1.272(5)$  g  $\text{cm}^{-3}$ ,  $D_c = 1.273$  g  $\text{cm}^{-3}$ ,  $\mu = 0.6$   $\text{cm}^{-1}$  (Mo- $K_\alpha$ ), final  $R = 0.047$ .

*Crystal Data for the  $\beta$ -Form of Z-Aib-OH.*— $\text{C}_{12}\text{H}_{15}\text{NO}_4$ ,  $M = 237.2$ . Orthorhombic,  $a = 15.965(4)$ ,  $b = 13.021(4)$ ,  $c = 12.544(4)$  Å,  $V = 2\,607.6(1)$  Å<sup>3</sup>, space group  $P2_12_12_1$ ,  $Z = 8$ ,  $D_m = 1.206(5)$  g  $\text{cm}^{-3}$ ,  $D_c = 1.207$  g  $\text{cm}^{-3}$ ,  $\mu = 0.6$   $\text{cm}^{-1}$  (Mo- $K_\alpha$ ), final  $R$  value 0.055.

*Crystal Data for Z(Aib)<sub>2</sub>OH.*— $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5$ ,  $M = 322.4$ . Monoclinic,  $a = 5.793(1)$ ,  $b = 13.056(2)$ ,  $c = 22.080(3)$  Å,  $\beta = 91.6(6)^\circ$ ,  $V = 1\,669.3(1)$  Å<sup>3</sup>, space group  $P2_1/c$ ,  $Z = 4$ ,  $D_m = 1.283(5)$  g  $\text{cm}^{-3}$ ,  $D_c = 1.283$  g  $\text{cm}^{-3}$ , final  $R$  value 0.045.

*Crystal Data for (Z-Aib)<sub>2</sub>O.*— $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_7$ ,  $M = 456.5$ . Tetragonal,  $a = b = 12.638(5)$ ,  $c = 15.394(5)$  Å,  $V = 2\,458.7$  Å<sup>3</sup>, space group  $I4_1$  (n. 80) special position 2,  $Z = 4$ ,  $D_m = 1.225(5)$  g  $\text{cm}^{-3}$ ,  $D_c = 1.23$  g  $\text{cm}^{-3}$ , final  $R$  value 0.059.

*X-Ray Crystal Structure Determinations of the  $\alpha$ - and  $\beta$ -Forms of Z-Aib-OH, of Z(Aib)<sub>2</sub>OH, and (Z-Aib)<sub>2</sub>O.*—Crystals of the  $\alpha$ -form of Z-Aib-OH were grown from an ethyl acetate–light petroleum solution. Philips PW 1100 diffractometer,  $\omega$ -2 $\theta$  scan mode up to  $\theta = 25^\circ$ ; graphite-monochromated Mo- $K_\alpha$  radiation ( $\lambda = 0.710\,69$  Å); 2 168 unique reflections and 453 with  $I \geq 3\sigma(I)$  considered observed. The structure was solved with MULTAN 80<sup>24</sup> and refined by block-diagonal least-squares, with weights  $w = 1/0.5 [\sigma^2(F) + 0.000\,53 F^2]$ . The thermal parameters were anisotropic for all non-hydrogen atoms. The hydrogen atoms were found on a difference Fourier map and refined isotropically.

Crystals of the  $\beta$ -form of Z-Aib-OH were grown from an ethyl acetate–light petroleum solution. 2 560 Unique reflections were collected, 791 with  $I > 3\sigma(I)$  were considered observed; the hydrogen atoms were calculated and not refined. All other data are identical to those reported above for the  $\alpha$ -form of Z-Aib-OH. Crystals of Z(Aib)<sub>2</sub>OH were grown from an ethanol–water mixture by slow evaporation. CAD 4 Enraf–Nonius diffractometer,  $\omega$ -2 $\theta$  scan mode up to  $\theta = 70^\circ$ ; graphite-monochromated Cu- $K_\alpha$  radiation ( $\lambda = 1.5418$  Å); 3 276 unique reflections and 2 028 with  $I > 3\sigma(I)$ . The structure was solved with MULTAN 80<sup>24</sup> and refined by full-matrix least-squares,  $w = 1/\sigma(F^2)$ . The thermal parameters were anisotropic for all non-hydrogen atoms. The N–H and O–H hydrogens were located

on a difference Fourier map and refined isotropically. The positional parameters of the other hydrogen atoms in the molecule were calculated from the stereochemistry of the atoms to which they are linked. These hydrogen atoms were not refined and isotropic thermal parameters (equal to those of the carbon atoms to which they are linked) were assigned. Crystals of (Z-Aib)<sub>2</sub>O were grown from a diethyl ether–light petroleum solution. 1 122 Unique reflections and 875 with  $I > 3\sigma(I)$ ; the hydrogen atoms were not refined. All other data are identical to those reported above for the  $\alpha$ -form of Z-Aib-OH.

Tables of fractional atomic co-ordinates, bond lengths and angles, and torsion angles are available from the Cambridge Crystallographic Data Centre.

*<sup>1</sup>H Nuclear Magnetic Resonance.*—The <sup>1</sup>H n.m.r. spectra were recorded with a Bruker WP 200SY spectrometer. Measurements were carried out by using deuteriochloroform (99.96% D; Fluka) and dimethyl sulphoxide (99.96% D<sub>6</sub>; Fluka).

*Infrared Absorption.*—I.r. absorption spectra were recorded with a Perkin-Elmer model 580 B spectrophotometer equipped with a Perkin-Elmer model 3 600 data station and model 660 printer.

## Results and Discussion

*Chemistry.*—In agreement with literature data,<sup>2,3</sup> from the reaction mixture of Z-Cl and H-Aib-OH we were able to isolate two crystalline fractions of Z-Aib-OH having different melting ranges. The fraction with lower melting range ( $\alpha$ -form) was obtained in 63% yield, while the fraction with higher melting range ( $\beta$ -form) in 27% yield. The two forms of Z-Aib-OH have different solid-state i.r. absorption spectra in the N–H and C=O stretching regions, but show identical t.l.c. chromatographic behaviour and solution <sup>1</sup>H n.m.r. properties, strongly supporting the view that the crystal-packing modes, and in particular the hydrogen-bonding schemes, diverge in the two cases.

A third crystalline product was isolated from the same reaction mixture, although in very low yield, 1.5%. From comparison with literature data,<sup>2</sup> spectroscopic (i.r. absorption and <sup>1</sup>H n.m.r.) and t.l.c. chromatographic characterizations, and elemental analysis this product was identified as the Z-protected dipeptide, Z(Aib)<sub>2</sub>OH.

In order to obtain some insight on the variety of possible reactive intermediates responsible for the formation of Z(Aib)<sub>2</sub>OH,<sup>17–19</sup> Z-Aib-OH was treated with an equivalent of Z-Cl and triethylamine in anhydrous toluene (in the absence of H-Aib-OH). A crystalline compound was obtained in good yield (45%) which was identified as the symmetric anhydride, (Z-Aib)<sub>2</sub>O, again by comparison with literature data,<sup>3</sup> spectroscopic and chromatographic characterizations, and elemental analysis. Interestingly, the presence of this intermediate was also assessed chromatographically (t.l.c.), although to a limited extent, under the conditions which are typically used for the synthesis of Z-Aib-OH,<sup>2</sup> i.e. in aqueous acetone, pH 10.8–10.9, at room temperature. In addition, (Z-Aib)<sub>2</sub>O was shown to react smoothly with amino acid esters and *N*-deblocked peptides to give Aib-X peptide bond formation.<sup>3,25</sup> These data do not prove unequivocally that in our reaction mixture the dipeptide Z(Aib)<sub>2</sub>OH is formed *via* the intermediacy of the symmetric anhydride (Z-Aib)<sub>2</sub>O, but at least indicate that this is a reasonable route. The formation of (Z-Aib)<sub>2</sub>O is best explained by disproportionation of the mixed carboxylic carbonic anhydride Z-Aib-OZ,<sup>17–19</sup> formed, in turn, by nucleophilic attack of the Z-Aib-O<sup>−</sup> carboxylate anion on the carbonyl carbon atom of Z-Cl with displacement of the chloride ion.



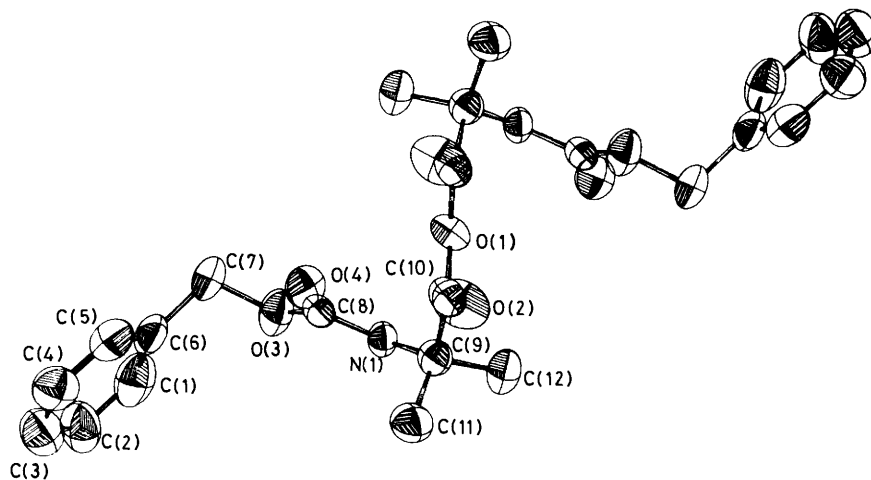


Figure 4. Molecular structure of  $(Z\text{-Aib})_2\text{O}$  with the numbering of the atoms of the asymmetric unit

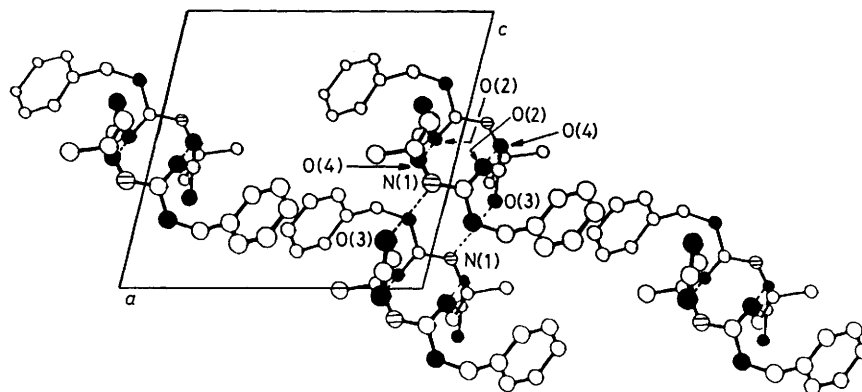


Figure 5. Crystal packing of the molecules of the  $\alpha$ -form of  $Z\text{-Aib-OH}$  viewed down the  $b$  axis. Intermolecular hydrogen bonds are indicated as dashed lines

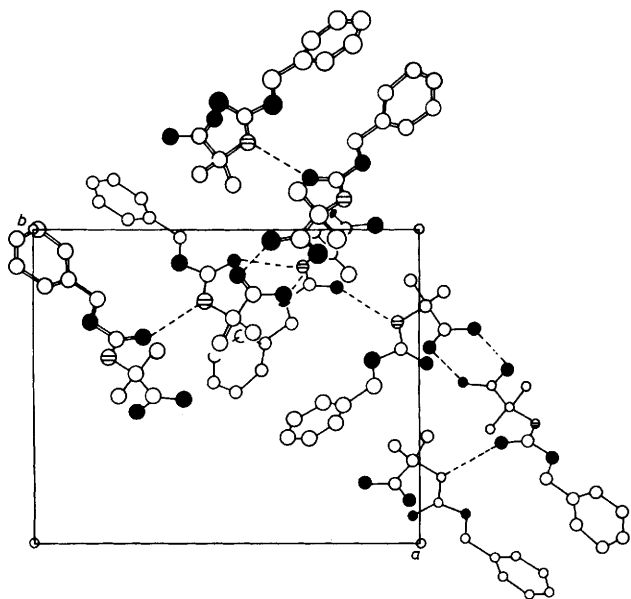


Figure 6. Crystal packing of the molecules of the  $\beta$ -form of  $Z\text{-Aib-OH}$  viewed down the  $c$  axis. Intermolecular hydrogen bonds are indicated as dashed lines

$\text{N}(1)\text{-C}(9)\text{-C}(10)$  and  $\text{N}(1)\text{-C}(9)\text{-C}(10)\text{-O}(4)$  have values typical for a folded conformation ( $47.6$  and  $39.3^\circ$  for the  $\alpha$ -form,

$59.4$  and  $38.7^\circ$  for molecule A of the  $\beta$ -form, and  $56.6$  and  $42.4^\circ$  for molecule B of the  $\beta$ -form). The carboxylic acid residues adopt a conformation with respect to the  $\text{C}(9)\text{-N}(1)$  bond intermediate between the anticlinal and antiplanar conformations,<sup>30</sup> the  $\text{N}(1)\text{-C}(9)\text{-C}(8)\text{-O}(3)$  torsion angle being  $-147.0$  ( $\alpha$ -form),  $-144.4$  ( $\beta$ -form, molecule A), and  $-139.9^\circ$  ( $\beta$ -form, molecule B). The angles between normals to the planes of the urethane and carboxylic acid groups are  $109.0$  for the  $\alpha$ -form,  $100.4$  for molecule A of the  $\beta$ -form, and  $102.0^\circ$  for molecule B of the  $\beta$ -form. There are no intramolecular hydrogen bonds in the molecules of either the  $\alpha$ -form or the  $\beta$ -form of  $Z\text{-Aib-OH}$ . There are, however, significant differences in the intermolecular hydrogen-bonding schemes of the two forms. The molecules of the  $\alpha$ -form are held together across a crystallographic centre of symmetry by the formation of a double intermolecular hydrogen bond of the  $\text{O-H}\cdots\text{O}$  (urethane) type, giving rise to a 14-membered ring cyclic dimer, as shown in Figure 5. The  $\text{O}(4)\cdots\text{O}(2)$  ( $2-x, \bar{y}, 2-z$ ) distances are  $2.65 \text{ \AA}$ .<sup>31,32</sup> Linear chains of molecules along the  $c$  axis are characterized by  $\text{N-H}\cdots\text{O}$  (acid) intermolecular hydrogen bonds, where the  $\text{N}(1)\cdots\text{O}(3)$  ( $x, \frac{1}{2}-y, -\frac{1}{2}+z$ ) distance is  $2.96 \text{ \AA}$ .<sup>33</sup> Dimer formation is also observed between molecules A and B of the  $\beta$ -form, but the intermolecular hydrogen bonds are of the  $\text{O-H}\cdots\text{O}$  (acid) type, giving rise to an eight-membered ring cyclic structure, as shown in Figure 2. The  $\text{O}(4)\text{B}\cdots\text{O}(3)\text{A}$  ( $2-x, y-\frac{1}{2}, \frac{1}{2}-z$ ) and  $\text{O}(3)\text{B}\cdots\text{O}(4)\text{A}$  ( $2-x, y-\frac{1}{2}, \frac{1}{2}-z$ ) distances are  $2.61$  and  $2.66 \text{ \AA}$ , respectively.<sup>31,32</sup> Additional hydrogen bonds involving the  $\text{N-H}$  group as donor

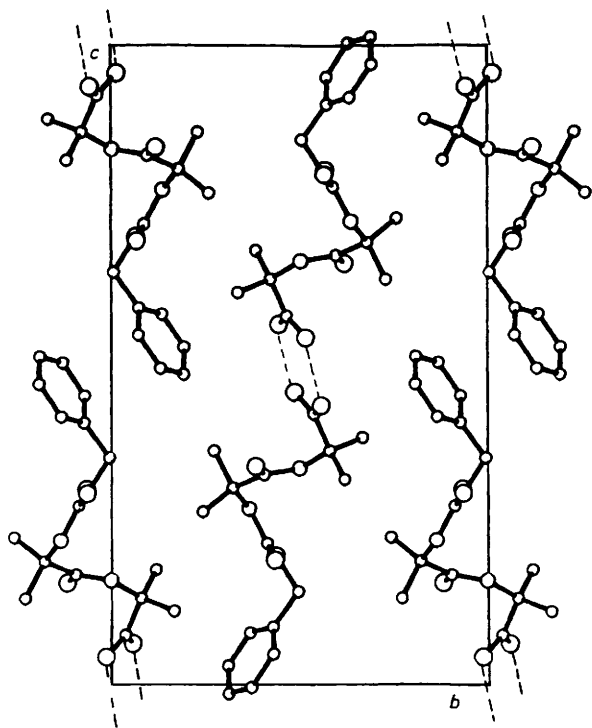
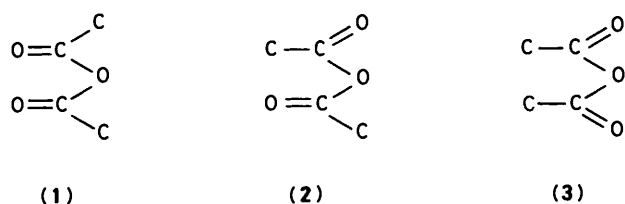


Figure 7. Crystal packing of the molecules of  $Z(\text{Aib})_2\text{OH}$  viewed down the  $a$  axis. Intermolecular hydrogen bonds are indicated as dashed lines



and the urethane carbonyl oxygen as acceptor are  $\text{O}(2)\text{A} \cdots \text{N}(1)\text{B}$  ( $x, y, z$ ) (2.93 Å)<sup>33</sup> and  $\text{O}(2)\text{B} \cdots \text{N}(1)\text{A}$  ( $\frac{1}{2} + x, \frac{3}{2} - y, 1 - z$ ) (3.10 Å)<sup>33</sup> (Figure 6). As for the structure of  $Z(\text{Aib})_2\text{OH}$ , the conformation of the benzyloxycarbonylamino moiety corresponds to one of the energy minima calculated for this group<sup>26</sup> (the  $\omega_0, \theta_1, \theta_2$ , and  $\theta_3$  torsion angles have values of 175.3, 175.5, 90.7, and 67.4°, respectively). The signs of the  $\text{Aib}, \phi, \psi$  torsion angles (65.9 and 26.2°) are opposite to those of the corresponding  $\text{Aib}_2$  angles (-49.4 and -45.5°), as typically found in folded  $\text{Aib}$  homopeptides.<sup>14-16</sup> The peptide CONH bond, as the aforementioned urethane CONH bond, can be considered planar, the pertinent  $\omega_1[\text{C}_1^2-\text{C}_1^1-\text{N}_2-\text{C}_2^1]$  torsion angle being 172.4°.

The molecules of  $Z(\text{Aib})_2\text{OH}$  are not stabilized by any intramolecular hydrogen bond. The  $\text{N}_2 \cdots \text{O}(2)$  intramolecular separation (3.33 Å) is at the upper limit of a  $\text{N} \cdots \text{O}$  hydrogen bond in amides,<sup>33</sup> but the directions of the  $\text{N}_2-\text{H}$  and  $\text{C}(8)=\text{O}(2)$  bonds are significantly different, the pertinent  $\text{C}(8)=\text{O}(2) \cdots \text{H}(\text{N}_2)$  and  $\text{O}_2 \cdots \text{H}(\text{N}_2)-\text{N}_2$  angles being 61.4 and 82.7°, respectively. Molecular packing of  $Z(\text{Aib})_2\text{OH}$  (Figure 7) is governed by a double intermolecular hydrogen bond of the  $\text{O}-\text{H} \cdots \text{O}(\text{acid})$  type (producing the eight-membered ring cyclic dimer characteristic of carboxylic acids), which holds the molecules together across a crystallographic centre of symmetry. The  $\text{O}(2) \cdots \text{O}_T$  ( $\bar{x} + 2, \bar{y} + 1, \bar{z} + 1$ ) distances are 2.62 Å.<sup>31,32</sup> These dimers are piled up and held together through  $\text{N} \cdots \text{O}$  hydrogen bonds involving the NH group of  $\text{Aib}_1$  and the carbonyl group of the same residue of a

molecule translated along the  $a$  axis [the  $\text{N}_1 \cdots \text{O}_1$  distance is 2.92 Å].<sup>33</sup> The other potential donor and acceptor groups,  $\text{N}_2-\text{H}$  and  $\text{C}(8)=\text{O}(2)$ , respectively, are not involved in the hydrogen-bonding scheme. This result is not in accord with the principle that the maximum number of proton donors and acceptors will participate in hydrogen bonds.<sup>34,35</sup> Additional forces operative in the molecular packing of  $Z(\text{Aib})_2\text{OH}$  along the  $a$  axis are van der Waals interactions between apolar groups, such as phenyl-phenyl, phenyl-methyl, and methyl-methyl interactions (Figure 7).

The anhydride moiety of  $(Z-\text{Aib})_2\text{O}$  is significantly non-planar, the angle between normals to the planes of  $\text{O}(2)-\text{C}(10)-\text{O}(1)$  and  $\text{O}(2)-\text{C}(10)-\text{O}(1)$  being 28.0°. The conformation of the anhydride moiety is type (1) (*trans-trans*), the value of the torsion angle  $\text{C}(9)-\text{C}(10)-\text{O}(1)-\text{C}(10)'$  being 172.1°. The intramolecular distance  $\text{O}(2) \cdots \text{O}(2)'$  would be 2.28 Å for a completely planar, type (1) anhydride with a bond angle  $\text{C}(10)-\text{O}(1)-\text{C}(10)'$  amounting to 110°. The observed torsion angle of 28.0° between the two parts of the anhydride moiety and the opening of the  $\text{C}(10)-\text{O}(1)-\text{C}(10)'$  bond angle to the experimentally found value of 120.7° increases the intramolecular distance  $\text{O}(2) \cdots \text{O}(2)'$  to the observed value of 2.73(2) Å, this separation being slightly lower than the van der Waals distance between non-bonded oxygen atoms. It seems, therefore, that the observed conformation of this type (1) anhydride is governed mainly by the steric interaction of  $\text{O}(2)$  and  $\text{O}(2)'$ .

The molecules of monochloroacetic anhydride<sup>28</sup> and  $(\text{Pht}-\text{Aib})_2\text{O}$ ,<sup>1</sup> the only other *acyclic* carboxylic anhydrides the structures of which have been solved by X-ray diffraction, also adopt type (1) conformation. In all known X-ray structures of *cyclic* carboxylic anhydrides,<sup>36</sup> conversely, the five- or six-membered annular systems force the anhydride moiety to assume type (3) (*cis-cis*) conformation. The exceptional type (2) (*cis-trans*) conformation, proposed for formic anhydride in the gas phase from an electron diffraction investigation,<sup>37</sup> is understandable in terms of intramolecular hydrogen bonding rather than steric factors.

The conformation of the benzyloxycarbonylamino moieties of  $(Z-\text{Aib})_2\text{O}$  also corresponds to one of the energy minima calculated for this group<sup>26</sup> (the  $\omega_0, \theta_1, \theta_2$ , and  $\theta_3$  torsion angles have values of -167.3, -174.0, -105.0, and -67.0°, respectively). The  $\text{Aib}$  residues adopt a folded conformation,<sup>14-16</sup> the values of the  $\phi, \psi$  torsion angles being -50.6 and -40.8°. The angle between normals to the planes of the urethane and phenyl groups is 59.5°, while that between the urethane and anhydride groups is 106.3°.

The only hydrogen bond in the packing of the  $(Z-\text{Aib})_2\text{O}$  molecules is of the intermolecular type, the  $\text{N}(1) \cdots \text{O}(4)$  (urethane) ( $\bar{x}, \frac{1}{2} + y, -\frac{1}{4} + z$ ) separation being 2.88 Å.<sup>33</sup>

## References

- Part 146, G. Valle, C. Toniolo, and G. Jung, *Liebigs Ann. Chem.*, in the press.
- M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, 1960, **11**, 29.
- W. J. McGahren and M. Goodman, *Tetrahedron*, 1967, **23**, 2017.
- E. Atherton, C. J. Logan, and R. C. Sheppard, *J. Chem. Soc., Perkin Trans. 1*, 1981, 538.
- E. Pedroso, A. Grandas, M. A. Saralegui, E. Giralt, C. Granier, and J. Van Rietschoten, *Tetrahedron*, 1982, **38**, 1183.
- E. Wünsch, in 'Peptides 1982,' eds. K. Blaha and P. Malon, de Gruyter, Berlin, 1983, p. 55.
- M. Tessier, F. Albericio, E. Pedroso, A. Grandas, R. Eritja, E. Giralt, C. Granier, and J. Van Rietschoten, *Int. J. Peptide Protein Res.*, 1983, **22**, 125.
- E. Giralt, R. Eritja, A. Grandas, E. Pedroso, M. Tessier, E. Albericio, C. Granier, and J. Van Rietschoten, in 'Peptides 1984,' ed. U. Ragnarsson, Almquist and Wiksell, Stockholm, 1984, p. 173.

- 9 F. Albericio and G. Barany, *Int. J. Peptide Protein Res.*, 1984, **23**, 342.
- 10 W. D. Fuller, G. F. Sigler, N. C. Chaturvedi, and M. S. Verlander, in 'Peptides: Structure and Function,' eds. V. J. Hruby and D. H. Rich, Pierce, Rockford, 1983, p. 79.
- 11 G. Sigler, W. D. Fuller, N. C. Chaturvedi, M. Goodman, and M. Verlander, *Biopolymers*, 1983, **22**, 2157.
- 12 L. Lapatsanis, G. Milias, K. Froussios, and M. Kolovos, *Synthesis*, 1983, 671.
- 13 J. W. van Nispen, J. P. Polderijk, and H. M. Greven, *Recl. Trav. Chim. Pays-Bas*, 1985, **104**, 99.
- 14 E. Benedetti, C. Pedone, and C. Toniolo, in 'Peptides 1980,' ed. K. Brunfeldt, Scriptor, Copenhagen, 1981, p. 619.
- 15 E. Benedetti, A. Bavoso, B. Di Blasio, V. Pavone, C. Pedone, M. Crisma, G. M. Bonora, and C. Toniolo, *J. Am. Chem. Soc.*, 1982, **104**, 2437.
- 16 C. Toniolo, G. M. Bonora, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, and C. Pedone, *Biopolymers*, 1983, **22**, 205.
- 17 R. B. Merrifield, A. R. Mitchell, and J. E. Clarke, *J. Org. Chem.*, 1974, **39**, 660.
- 18 J. Meienhofer, in 'The Peptides: Analysis, Synthesis, Biology,' eds. E. Gross and J. Meienhofer, Academic Press, New York, 1979, vol. 1, p. 263.
- 19 S. Kim, J. I. Lee, and Y. C. Kim, *J. Org. Chem.*, 1985, **50**, 560.
- 20 W. Mayr, G. Jung, and J. Strähle, *Liebigs Ann. Chem.*, 1980, 715.
- 21 G. Valle, G. M. Bonora, and C. Toniolo, *Can. J. Chem.*, 1984, **62**, 2661.
- 22 G. Valle, G. M. Bonora, and C. Toniolo, *Gazz. Chim. Ital.*, 1984, **114**, 487.
- 23 P. Van Roey, G. D. Smith, T. M. Balasubramanian, and G. R. Marshall, *Acta Crystallogr.*, 1983, **C39**, 894.
- 24 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.P. Declercq, and M. M. Woolfson, 'MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data.'
- 25 C. Toniolo, G. M. Bonora, M. Crisma, and F. Formaggio, unpublished observations.
- 26 E. Benedetti, C. Pedone, C. Toniolo, M. Dudek, G. Némethy, and H. A. Scheraga, *Int. J. Peptide Protein Res.*, 1983, **21**, 163.
- 27 Y. Paterson, S. M. Rumsey, E. Benedetti, G. Némethy, and H. A. Scheraga, *J. Am. Chem. Soc.*, 1981, **103**, 2947.
- 28 A. J. De Kok and C. Romers, *Recl. Trav. Chim. Pays-Bas*, 1969, **88**, 625.
- 29 IUPAC-IUB Commission on Biochemical Nomenclature, *Biochemistry*, 1970, **9**, 3471.
- 30 J. D. Dunitz and P. Strickler, in 'Structural Chemistry and Molecular Biology,' eds. A. Rich and N. Davidson, Freeman, San Francisco, 1968, p. 595.
- 31 I. D. Brown, *Acta Crystallogr.*, 1976, **A32**, 24.
- 32 J. Mitra and C. Ramakrishnan, *Int. J. Peptide Protein Res.*, 1977, **9**, 27.
- 33 C. Ramakrishnan and N. Prasad, *Int. J. Protein Res.*, 1971, **3**, 209.
- 34 M. C. Etter, *J. Am. Chem. Soc.*, 1982, **104**, 1095.
- 35 Z. Berkovitch-Yellin, S. Ariel, and L. Leiserowitz, *J. Am. Chem. Soc.*, 1983, **105**, 765.
- 36 F. H. Allen, *Acta Crystallogr.*, 1981, **B37**, 900.
- 37 A. Boogard, H. J. Geise, and F. C. Mijlhoff, *J. Mol. Struct.*, 1972, **13**, 53.

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