Crystal Structures of Protected Derivatives of α-Alkoxyglycines

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X-ray crysal structures of two α-alkoxyglycine derivatives, Cbz–Gly(OR)–OR (R = Me and Pr^i), were determined. The structural and chemical characteristics of Gly(OR) residues as unique β-oxa analogs of α-amino acids are discussed.

α-Alkoxyglycines are unique α-amino acids possessing an oxygen atom directly attached to the α-carbon atom (Chart 1). Their protected derivatives, Cbz–Gly(OR)–OR′, were prepared from the corresponding derivatives of *N*-chloroglycine or α-hydroxyglycine.[1–3] Although the N-unprotected forms of the Gly(OR) derivatives are too labile to be used as amino components for peptide bond formation under normal conditions, we developed a method for synthesizing Gly(OR)-containing peptides which involved in situ hydrogenolytic deprotection of the Cbz group.[1] On the other hand, the N-protected free acids, Cbz–Gly(OR)–OH, are stable enough to be subjected to optical resolution and the determination of their absolute configurations established the usefulness of these amino acid derivatives as building blocks for the synthesis of unique peptide analogs.[4,5] Here we describe the crystal structures of two protected racemic alkoxyglycines, Cbz–Gly(OMe)–OMe (**1**) and Cbz–Gly(OPr^i)–OPr^i (**2**).

Colorless prismatic crystals of the methoxy and isopropoxy compounds, **1** and **2**, suitable for X-ray analysis were obtained from the MeOH and Pr^{i}OH solutions, respectively. Crystallographic data of **1** and **2** are summarized in Table 1. The unit cell of **1** contains four molecules, two (*R*)- and two (*S*)-enantiomers, while in the case of **2**, two molecules composed of each enantiomer are contained in the unit cell. The molecular structures of the (*S*)-enantiomers of **1** and **2** are shown in Fig. 1,

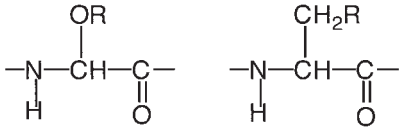

Chart 1.

Table 1. Crystallographic Data for **1** and **2**

	1	**2**
Formula	$C_{12}H_{15}NO_5$	$C_{16}H_{23}NO_5$
Fw	253.25	309.36
Crystal size/mm	0.25 × 0.15 × 0.10	0.20 × 0.30 × 0.30
Crystal system	orthorhombic	triclinic
Space group	$Pca2_1$	$P\bar{1}$
a/Å	12.956(2)	5.511(1)
b/Å	11.548(1)	10.629(3)
c/Å	8.445(2)	15.110(5)
α/°	90.0	73.34(2)
β/°	90.0	88.00(2)
γ/°	90.0	80.57(2)
V/Å^3	1263.5	836.4
d_{calc}/g cm^{-3} (Z)	1.331 (4)	1.228 (2)
F_{000}	536.0	332.0
μ(Cu Kα)/mm^{-1}	0.839	0.716
No. of reflections	949	2357
R (wR)	0.0445 (0.0397)	0.0633 (0.0795)

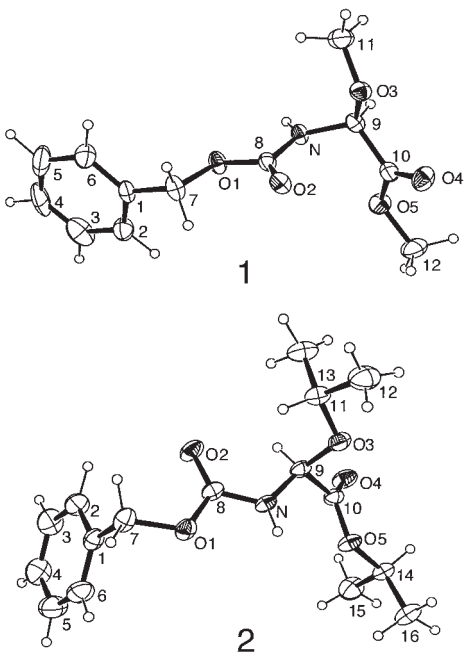

Fig. 1. The molecular structures of **1** and **2** in the crystals with atomic numberings. The (*S*)-enatiomers are shown.

and the selected bond length and angle values are summarized in Table 2. While the side chain alkoxy groups adopt a g^- conformation in both structures **1** and **2**, the two Gly(OR) residues adopt completely different molecular conformations from each other, i.e., the (ϕ, ψ) values are (58°, 48°) in **1** and (−137°, −36°) in **2**. However, the difference might be due to molecular packing in the crystals, as their stereochemistry in solution is considered to be similar, since the $J_{NH-\alpha H}$ values in the ^{1}H NMR spectra are invariably about 9 Hz for Cbz–Gly(OR)–OR′ with various R and R′ groups.[4,5]

α-Alkoxyglycines are considered to be β-oxa analogs of α-amino acids. In one case, the Gly(OPr^i) residue actually corresponds to the β-oxa analog of the proteineous Leu residue. The stereochemical similarity of Gly(OPr^i) and Leu is obvious, and

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Table 2. Selected Bond Lengths (Å) and Valence and Torsion Angles (°) for **1** and **2**

Bond	**1**	**2**
C7–O1	1.466(6)	1.467(3)
O1–C8	1.354(5)	1.327(3)
C8–O2	1.215(6)	1.217(3)
C8–N	1.336(6)	1.349(2)
N–C9	1.451(5)	1.432(3)
C9–C10	1.530(6)	1.513(3)
C9–O3	1.420(5)	1.409(3)
O3–C11	1.414(6)	1.448(2)
C10–O4	1.203(6)	1.206(3)
C10–O5	1.326(6)	1.329(2)
O5–C*x*[a)]	1.444(6)	1.465(2)
Angle	**1**	**2**
C7–O1–C8	114.8(4)	115.9(1)
O1–C8–N	110.3(4)	111.7(2)
O2–C8–N	125.4(4)	124.3(2)
C8–N–C9	120.8(4)	121.3(2)
N–C9–C10	112.4(3)	113.1(2)
N–C9–O3	112.8(3)	113.9(2)
C10–C9–O3	106.6(4)	103.9(1)
C9–O3–C11	114.4(4)	114.8(2)
C9–C10–O4	124.6(4)	123.4(2)
C9–C10–O5	110.3(4)	112.0(2)
C10–O5–C*x*[a)]	115.2(4)	118.5(1)
Angle	**1**[b)]	**2**[b)]
C7–O1–C8–N	−173.8(4)	−178.7(2)
O1–C8–N–C9	173.7(3)	−179.3(2)
C8–N–C9–C10 (ϕ)	58.4(5)	−136.7(2)
N–C9–C10–O5 (ψ)	47.5(5)	−35.5(2)
N–C9–O3–C11 (χ)	−68.7(5)	−76.0(2)
C9–C10–O5–C*x*[a)]	173.2(4)	−177.0(2)

a) C*x* refers to C12 for **1** and C14 for **2**. b) Torsion angle values of the (*S*)-enantiomer.

the observed C_α–O–C_γ angle (115°) of **2** is very close to the standard value of the corresponding C_α–C_β–C_γ angle of the Leu residue (116°),[6] although the C_α–O and O–C_γ bond lengths (1.41 and 1.45 Å, respectively) are appropriately smaller than the normal C(sp^3)–C(sp^3) bond length (1.54 Å).

Peptide analogs containing the Gly(OR) residue are expected to exhibit stereochemical characteristics essentially similar to those of the parent peptides. The relative opioid activity of the D- and L-Gly(OMe) residue-containing dermorphin tetrapeptide analogs corresponded well to that of the parent tetrapeptide containing a D-Ala residue and its diastereomer possessing an L-Ala residue.[4] On the other hand, the Gly(OR) residues are considered to possess at least two unique characteristics due to the presence of an oxygen atom at the β-position, i.e., the lability in their free amino state, and the hydrogen-bonding ability at the β-position. As for the latter characteristic, a significant difference in the silica-gel thin-layer chromatographic behavior was observed between Cbz–Gly(OPr^i)–OH and Cbz–Leu–OH. The R_f values in $CHCl_3$–MeOH–AcOH (92:5:3)[7] were 0.28 and 0.16 for the Gly(OPr^i) and Leu derivatives, respectively. Since the esters Cbz–Gly(OPr^i)–OPr^i and Cbz–Leu–OPr^i showed the same R_f value (0.75) in $CHCl_3$–MeOH (99:1), the higher R_f value of the free carboxyl form, Cbz–Gly(OPr^i)–OH, is explained by the five-membered cyclic structure, in which the carboxyl group is intramolecularly hydrogen-bonded to the β-oxygen atom.

Experimental

According to the reported procedures, Cbz–Gly(OMe)–OMe was synthesized from Cbz–Gly–OMe via the *N*-chloro derivative,[1] and Cbz–Gly(OPr^i)–OPr^i from Cbz–Gly(OH)–OH.[2] Cbz–L-Leu–OPr^i was prepared by the condensation of Cbz–L-Leu–OH and Pr^{i}OH in $CHCl_3$ using dicyclohexylcarbodiimide and 4-dimethylaminopyridine. Silica-gel thin-layer chromatography was performed using Kieselgel 60F_{254} Art. 5717 (Merck).

Intensity data were collected at 295 K on a Rigaku AFC-5RU refractometer, equipped with a rotating anode, using graphite-monochromated Cu Kα radiation ($\lambda = 1.54178$ Å) in a ω–2θ scanning mode, within a range of $2\theta < 120°$. The data were corrected for Lorentz and polarization factors, but not for absorption. The reflections with $F_0 > 3\sigma$ were used for the calculation. The structures were solved with MULTAN78[8] and refined by the block-diagonal least-squares method, based on F^2 ($w = [\sigma(F) + (0.023F)^2]^{-1}$), using the program system KPPXRAY.[9] Non-hydrogen atoms were refined anisotropically. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition numbers CCDC 213938 and 213939.

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