X-Ray Diffraction Structure Determination of a Novel Peptide Oxazol-5(4*H*)-one with a Chiral Carbon Atom in the Heterocyclic Moiety

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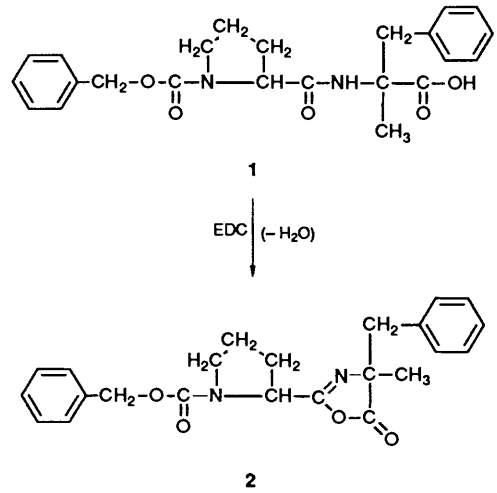
The X-ray diffraction structure analysis of a novel peptide oxazol-5(4*H*)-one with a chiral carbon atom in the heterocyclic moiety has been performed for the Z-L-Pro-L-(αMe)Phe-OH oxazolone.

A well understood mechanism explaining the loss of optical purity in reaction between the CO_2H group of N^{α}-acylated protein amino acids or peptides and nucleophiles involves the formation of oxazol-5(4*H*)-ones,[1] which are known to racemize (or epimerize) easily.[2] This interpretation of the α-inversion process was first put forward by Bergmann and Zervas[3] as early as 1928.

In view not only of their optical lability but also of their good electrophilic properties, it is not surprising that these intermediates would be amenable to direct analysis only with great difficulty.[4] However, by taking advantage of the excellent chemical and optical stabilities and high crystallinity of oxazol-5(4*H*)-ones from $C^{\alpha,\alpha}$-disubstituted α-amino acids, for the first time we have been able to get detailed information by X-ray diffraction of a peptide oxazolone with a chiral carbon atom in the heterocyclic moiety, namely the oxazolone from Z-L-Pro-L-(αMe)Phe-OH [Z, benzyloxycarbonyl; (αMe)Phe, C^{α}-methyl phenylalanine]. In this paper we discuss the most significant parameters characterizing this structure.

The oxazolone **2** was obtained in excellent yield (90%) by treatment of the *N*-protected dipeptide Z-L-Pro-L-(αMe)Phe-OH[5] **1** with *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC) hydrochloride in anhydrous acetonitrile according to Scheme 1.† Single crystals, suitable for a X-ray diffraction analysis, were grown from toluene–light petroleum.



Scheme 1

As shown in Fig. 1,‡[6] the tertiary urethane moiety is in the *trans*, *cis* conformation[9] [C-7–O-1–C-8–N-1(θ^1) = 179.5(4)°, 0-1–C-8–N-1–C-12(ω_0) = −4.4(7)°], while the Pro residue is semi-extended[10] [C-8–N-1–C-12–C-13(φ_1) = −55.9(7)°; N-1–C-12–C-13–N-2("ψ_1") = 139.7(5)°].[11] The values for the N-2–C-15–C-17–C-18(χ^1), C-15–C-17–C-18–C-19($\chi^{2,1}$) and C-15–C-17–C-18–C-23($\chi^{2,2}$) torsion angles of the (αMe)Phe side chain[12,13] are 56.7(6)°, 89.8(7)° and −86.8(7)°, a common observation for aromatic α-amino acids.[14]

The displacements of the atoms in the nearly planar oxazolone ring from its mean plane vary from −0.013 to 0.008 Å. The C-16 and C-17 atoms (both linked to the C-15 atom) are displaced on the opposite sides of the average plane of the ring by 1.236 and −1.308 Å, respectively. The exocyclic O-4 and C-12 atoms deviate from the plane by 0.029 and −0.067 Å, respectively. The C-13–N-2 bond length, 1.254(6) Å, is appropriate for a C–N double bond. This finding confirms the results obtained in the X-ray diffraction analyses of the amino acid and peptide oxazolones (from achiral $C^{\alpha,\alpha}$-disubstituted glycines) reported to date.[15–21] The C-13–O-3 and C-14–O-3 bond lengths [1.385(6) and 1.369(7) Å, respectively] indicate that the effect of electron delocalization is small, though significant.[22,23] The C-15–N-2 and C-15–C-14 bond lengths [1.458(6) and 1.526(7) Å, respectively] are close to those expected for a sp^3-hybridized C-15 atom.

The exocyclic bond angles about the carbonyl group C-14=O-4 of the lactone moiety differ by 5.9°, with a larger value for the C-15–C-14–O-4 bond angle, 129.9(5)°.[22,23] This latter value is probably the result of intramolecular interactions between the two substituents on the C-15 and the O-4 atoms. An additional

† *Z-L-Pro-L-(αMe)Phe-OH oxazolone:* m.p. 98–99 °C (from toluene–light petroleum); $[\alpha]_D^{20}$ −143.3 (*c* 0.5, $MeCO_2Et$); TLC (silica gel plates 60F–254, Merck) R_{f1} ($CHCl_3$–EtOH, 9:1) 0.65, R_{f2} (toluene–EtOH, 7:1) 0.70. Amino acid analysis (C. Erba model 3A 29): Pro 0.98, (αMe)Phe 1.02. $\nu_{max}(CDCl_3)/cm^{-1}$ 1817, 1702 and 1680 (shoulder) (Found: C, 70.2; H, 6.2; N, 7.1. Calc. for $C_{23}H_{24}N_2O_4$: C, 70.4; H, 6.2; N, 7.1).

‡ *Crystal Data for* **2**.—(From toluene–light petroleum): orthorhombic, space group $P2_12_12_1$, a = 19.492(2), b = 17.098(2), c = 6.305(1) Å, V = 2101.8(5) Å^3, T = 293 K, Z = 4, D_x = 1.240 Mg m^{-3}, D_m = 1.23 Mg m^{-3} (flotation), $F(000)$ = 832. Intensity data were collected on a Philips PW 1100 diffractometer, θ–2θ scan mode to 2θ = 56°, using MoKα graphite-monochromatized radiation (λ = 0.710 69 Å). The h, k, l ranges used for diffraction measurements were 0–25, 0–22 and 0–8, respectively. Data were corrected for Lorentz-polarization and absorption effects. The structure was solved by direct methods using the SHELXS 86 program[7] and refined by blocked least-squares. The thermal parameters of all non-hydrogen atoms were anisotropic. Hydrogen atoms, partially located on a ΔF map and partially calculated, were refined isotropically. The final conventional R factor for the 1247 reflections considered observed [$F \geq 7\sigma(F)$] was 0.050; R_w = 0.056 with $w = 1/[\sigma^2(F) + 0.004\,F^2]$. For all calculations the SHELX 76 program[8] was used. Coordinates and diagrams correspond to the (*L*, *L*) or (*S*, *S*) absolute configuration of the dipeptide oxazol-5(4*H*)-one. Atomic coordinates, bond lengths and bond angles, torsion angles, and thermal parameters are available on request from the Cambridge Crystallographic Data Centre. [See 'Instructions for Authors (1991)', *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1.]

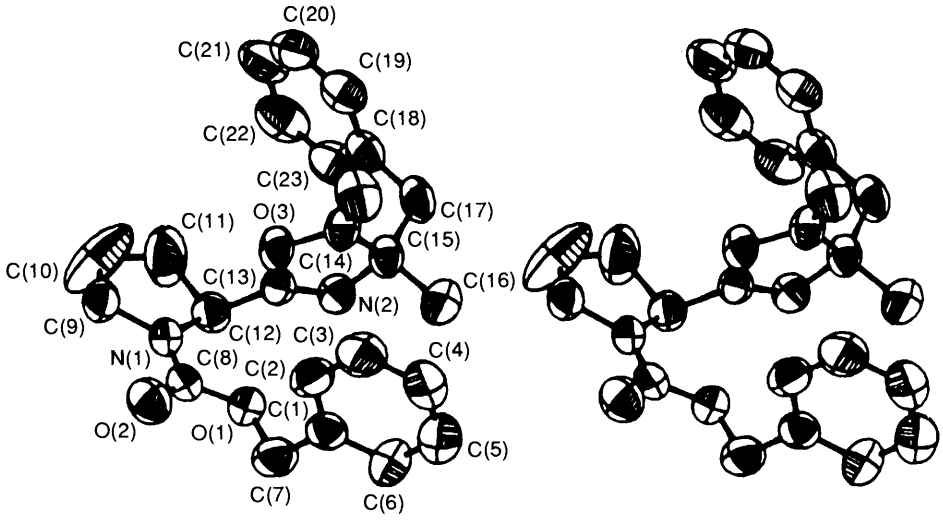
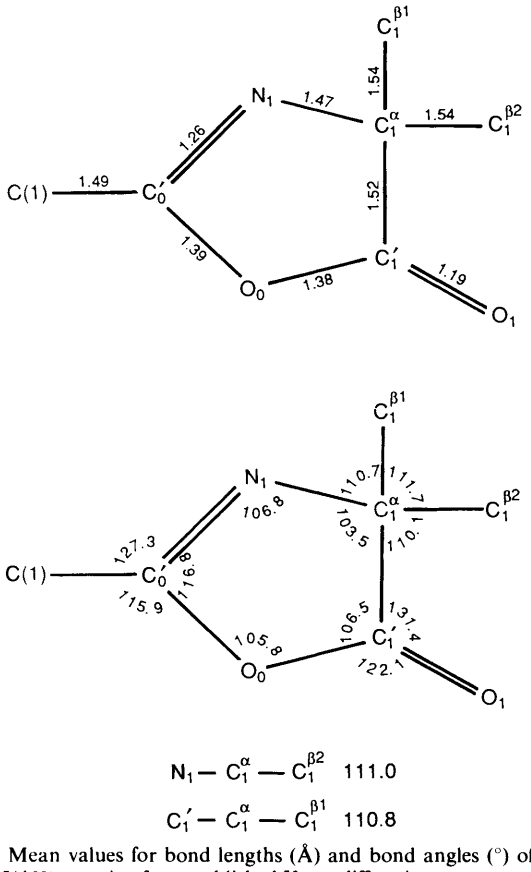


Fig. 1 An ORTEP[6] stereoview of oxazol-5(4*H*)-one **2** with atomic numbering. Non-hydrogen atoms are depicted as 50% probability ellipsoids.



$N_1 - C_1^{\alpha} - C_1^{\beta 2}$ 111.0

$C_1' - C_1^{\alpha} - C_1^{\beta 1}$ 110.8

Fig. 2 Mean values for bond lengths (Å) and bond angles (°) of the oxazol-5(4*H*)-one ring from published X-ray diffraction structures

relevant property is the widening of the C-12–C-13–N-2 bond angle to 127.8(5)°. The geometrical parameters of the oxazol-5(4*H*)-one ring, as averaged from published X-ray diffraction structures,[15-21] are reported in Fig. 2.

The oxazolone ring of **2** is nearly sandwiched between the two phenyl rings, making an angle of 146.5(2)° with the phenyl ring of the benzyloxycarbonyl group and of 126.2(2)° with the phenyl ring of the (αMe)Phe side chain. The dihedral angle between the two phenyl rings is 24.4(2)°. In all probability, the strong intramolecular dipole–dipole interactions between the oxazolone and the phenyl rings lead to attractions which more than compensate for the steric repulsion due to crowding. The

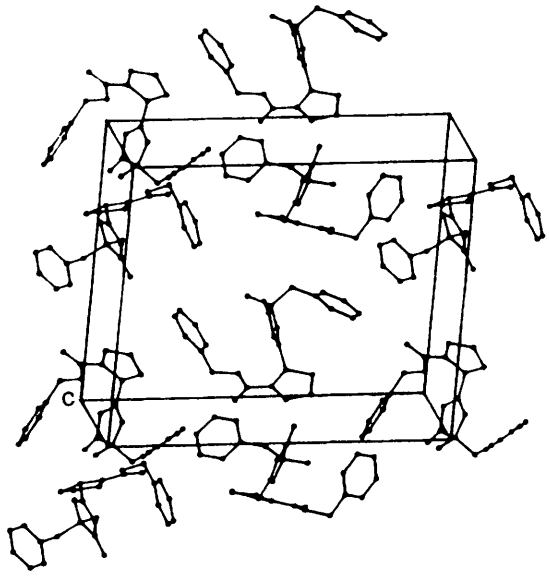


Fig. 3 Crystal packing of the molecules of oxazol-5(4*H*)-one **2**

folding of the aromatic moiety over the hydantoin[24] and 2,5-dioxopiperazine[25] rings of Phe derivatives and peptides is well documented.

A packing diagram of the molecules of oxazol-5(4*H*)-one **2** in the crystal is illustrated in Fig. 3.

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