methyl-MMdCyd and N^4-amino-dCyd have a *cis* relationship between the N^4-substituent and N(3).

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Structure of N-*tert*-Butoxycarbonyl-D-prolyl-L-prolyl-D-proline Methyl Ester, a Triproline Derivative with Alternating Configurations

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Abstract. $C_{21}H_{33}N_3O_6$, $M_r = 423.5$, orthorhombic, $P2_12_12_1$, $a = 12.610 (1)$, $b = 15.773 (3)$, $c = 11.670 (1)$ Å, $V = 2321.1 (9)$ Å^3, $Z = 4$, $D_x = 1.21$ g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 6.97$ cm^{-1}, $F(000) = 912$, room temperature, final $R = 0.050$ for 1770 independent reflections and 271 parameters.

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$C_{21}H_{33}N_3O_6$

The stereosequence of the ω angles in the main chain of the tripeptide is cis, cis, trans. This gives the molecule a shape different from those displayed by the homologous di- and tetrapeptides, whose conformations are similar.

Introduction. Recently, there has been much interest in linear oligopeptides and polypeptides with alternating L and D configurations, owing to their close relationship to some naturally occurring peptide and depsipeptide antibiotics which allow selective ion transport across natural and artificial membranes. Valinomycin and gramicidin A are the best known representatives of the two fundamental types of ionophores: ion carriers and channel-forming structures (Ascoli, De Santis, Palleschi & Rizzo, 1975; Benedetti, Di Blasio, Pedone, Lorenzi, Tomasic & Gramlich, 1979). Particular attention has been paid to the homo-oligoprolines owing to their importance as crucial components of many biological macromolecules (Benedetti, Bavoso, Di Blasio, Pavone, Pedone, Toniolo & Bonora, 1983). More recently, homo-oligoprolines with different chiral sequences have been studied (Benedetti, Di Blasio, Pavone, Pedone, Toniolo & Bonora, 1980; De Santis, Palleschi, Savino & Scipioni, 1985; De Santis, Palleschi, Savino, Scipioni, Sesta & Verdini, 1985). Here we report the X-ray analysis of the title tripeptide whose structure may be usefully compared with those of the analagous diproline (Benedetti et al., 1980) and tetraproline (Colapietro, De Santis, Palleschi & Spagna, 1986) derivatives with alternating configurations, in order to better define the conformational variability of this kind of polypeptide chain with chain length.

Experimental. A prismatic crystal ($0.1 \times 0.2 \times 0.4$ mm), elongated along **b**, was used for data collection on an Enraf–Nonius CAD-4 automatic diffractometer. Ni-filtered Cu $K\alpha$ radiation was used. The refined unit-cell parameters and the orientation matrix for the data collection were obtained by a least-squares fitting of the setting values of 25 reflections in the range $10 \le \theta \le 13°$. Out of a total 2646 independent reflections measured by the ω/θ-scan technique with $\theta \le 68°$, 1770 having $I_o > 3\sigma(I_o)$ were taken as observed and used in the structure determination. Index ranges: $0 \le h \le 15$, $0 \le k \le 19$, $0 \le l \le 14$. Three monitoring reflections (404, 124, 282) showed no significant intensity variation throughout the data collection. Lp correction applied, absorption ignored. The structure was solved by MULTAN80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) with default parameters except for the use of 320 E's instead of 270. Out of 24 sets of phases, the program calculated only eight since it recognized the eighth as correct. The corresponding E map showed, with only one

Table 1. *Fractional atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($\mathring{A}^2 \times 10$) *of non-H atoms with e.s.d.'s in parentheses*

$$B_{eq} = (4/3)\Sigma_i\Sigma_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
C(A31)	6369 (4)	9264 (4)	6312 (5)	84 (1)
C(A32)	7322 (5)	10114 (4)	7751 (5)	82 (1)
C(A33)	7520 (6)	8546 (4)	7717 (5)	96 (2)
C(A2)	7342 (3)	9316 (3)	7005 (3)	51 (1)
O(A2)	8289 (2)	9477 (2)	6287 (2)	50 (1)
O(A1)	8122 (3)	8272 (2)	5239 (3)	70 (1)
C(A1)	8612 (3)	8888 (2)	5534 (3)	47 (1)
N(1)	9584 (3)	9083 (2)	5124 (3)	50 (1)
C(1A)	10210 (3)	9805 (2)	5508 (3)	47 (1)
C(1B)	11259 (4)	9688 (3)	4845 (4)	61 (1)
C(1C)	10964 (4)	9170 (4)	3816 (5)	87 (1)
C(1D)	10099 (4)	8580 (3)	4241 (4)	62 (1)
C(1)	10423 (3)	9771 (2)	6796 (3)	48 (1)
O(1)	10700 (3)	9100 (2)	7239 (3)	67 (1)
N(2)	10346 (3)	10481 (2)	7399 (3)	49 (1)
C(2A)	9889 (3)	11302 (2)	7034 (3)	45 (1)
C(2B)	9801 (4)	11800 (3)	8150 (3)	60 (1)
C(2C)	10696 (5)	11458 (3)	8866 (4)	71 (1)
C(2D)	10695 (4)	10517 (3)	8604 (4)	60 (1)
C(2)	10594 (3)	11737 (2)	6146 (3)	42 (1)
O(2)	11531 (2)	11552 (2)	6038 (3)	59 (1)
N(3)	10137 (3)	12338 (2)	5506 (2)	46 (1)
C(3A)	10741 (4)	12739 (3)	4608 (3)	54 (1)
C(3B)	10037 (6)	13472 (3)	4262 (4)	97 (1)
C(3C)	8993 (4)	13315 (4)	4711 (6)	95 (2)
C(3D)	9030 (3)	12636 (3)	5546 (4)	58 (1)
C(3)	10931 (3)	12128 (3)	3642 (3)	48 (1)
O(31)	10436 (3)	11487 (2)	3465 (3)	71 (1)
O(32)	11705 (2)	12410 (2)	2967 (2)	56 (1)
C(32)	11965 (4)	11887 (3)	1972 (4)	65 (1)

spurious peak, all non-H atoms. Their coordinates were refined by a least-squares procedure with individual temperature factors, initially isotropic and then anisotropic. Full-matrix least squares minimized $\Sigma w(\Delta F)^2$, where $w = 1/\sigma^2(F)$. The H atoms, generated at the expected positions taking into account the results of the ΔF synthesis for the methyl groups, were included in the final refinement using a riding model with isotropic thermal factors 1.3 times the B_{eq}'s of the ridden atoms. 271 refined parameters included an overall scale factor and positional and anisotropic thermal parameters of the non-H atoms. Final $R = 0.050$, $wR = 0.066$, $S = 1.84$. Final $\Delta/\sigma_{max} = 0.01$; final difference electron density within ± 0.24 e Å^{-3}.

Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). All calculations, except those involving MULTAN80, were performed with the Enraf–Nonius (1979) system of programs (SDP) on a VAX 750 computer of the Centro di Metodologie Chimico-fisiche dell' Università di Napoli.

Final atomic parameters of the non-H atoms are listed in Table 1.*

Discussion. A view of the molecule with the atom-labelling scheme is shown in Fig. 1. Bond lengths and valence angles are presented in Table 2. Apart from a few values for the pyrrolidine ring Pro3, which will be discussed later, all bond lengths and angles compare well with the average values for similar compounds (Benedetti *et al.*, 1983).

The crystal packing, governed only by van der Waals forces, does not show abnormal intermolecular contacts.

The conformational parameters are presented in Table 3.

Backbone conformation

The backbone conformation of a polypeptide chain is commonly expressed in terms of the angles φ_i, ψ_i and ω_i. For the backbone atom sequence $-C'_{i-1}-N_i-C^\alpha_i-C'_i-N_{i+1}-C^\alpha_{i+1}-C'_{i+1}-$ they are defined respectively as the torsion angles $C'_{i-1}-N_i-C^\alpha_i-C'_i$, $N_i-C^\alpha_i-C'_i-N_{i+1}$ and $C^\alpha_i-C'_i-N_{i+1}-C^\alpha_{i+1}$. The partial double-bond character of the peptide bond prevents rotation and freezes the values of ω at $0°$ (*cis*-peptide form) or $180°$ (*trans*-peptide form). With a secondary N atom the *trans* form is energetically favoured with respect to the *cis* form. But when the $(i+1)$th residue involves a tertiary N atom, as in proline, ω_i can take both values. It is well known that poly-L-proline can occur either with the *trans*-peptide bond forming left-handed helices (poly-L-proline II) or with the *cis*-peptide bond forming right-handed helices (poly-L-proline I). The two structures can interconvert in solution.

When a proline residue is inserted in a polypeptide chain, the corresponding φ angle is restricted within a narrow range around $-68°$ (for the L residue)
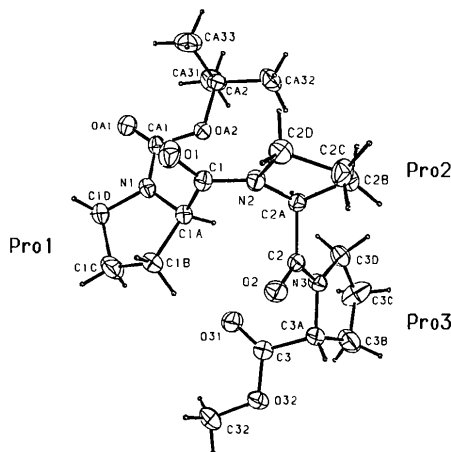

Fig. 1. *ORTEP* view of *tert*-Boc-D-Pro-L-Pro-D-proline methyl ester with the atom-labelling scheme. Thermal ellipsoids are drawn at 25% probability.

Table 2. *Bond lengths (Å) and valence angles (°)*

The ranges of the e.s.d.'s are 0·004–0·007 Å (mean 0·0047 Å) for the bond lengths and 0·3–0·4° (mean 0·31°) for the valence angles.

C(A2)—C(A33)	1·489		N(2)—C(2D)	1·475
C(A2)—C(A32)	1·531		C(2A)—C(2B)	1·525
C(A2)—C(A31)	1·472		C(2B)—C(2C)	1·505
C(A2)—O(A2)	1·481		C(2C)—C(2D)	1·515
C(A1)—O(A2)	1·343		C(2)—C(2A)	1·528
C(A1)—O(A1)	1·202		C(2)—O(2)	1·224
C(A1)—N(1)	1·351		C(2)—N(3)	1·337
N(1)—C(1A)	1·456		N(3)—C(3A)	1·442
N(1)—C(1D)	1·454		N(3)—C(3D)	1·474
C(1A)—C(1B)	1·544		C(3A)—C(3B)	1·512
C(1B)—C(1C)	1·498		C(3B)—C(3C)	1·438
C(1C)—C(1D)	1·516		C(3C)—C(3D)	1·450
C(1)—C(1A)	1·528		C(3)—C(3A)	1·502
C(1)—O(1)	1·230		C(3)—O(31)	1·207
C(1)—N(2)	1·326		C(3)—O(32)	1·330
N(2)—C(2A)	1·480		O(32)—C(32)	1·461
C(A31)—C(A2)—C(A32)	110·2		C(2A)—N(2)—C(2D)	110·9
C(A31)—C(A2)—C(A33)	112·8		N(2)—C(2A)—C(2B)	103·5
C(A31)—C(A2)—O(A2)	111·8		C(2A)—C(2B)—C(2C)	103·6
C(A32)—C(A2)—C(A33)	110·8		C(2B)—C(2C)—C(2D)	103·8
C(A32)—C(A2)—O(A2)	101·2		C(2C)—C(2D)—N(2)	103·3
C(A33)—C(A2)—O(A2)	109·5		N(2)—C(2A)—C(2)	111·2
C(A2)—O(A2)—C(A1)	119·7		C(2B)—C(2A)—C(2)	113·0
O(A2)—C(A1)—O(A1)	126·2		C(2A)—C(2)—O(2)	121·6
O(A2)—C(A1)—N(1)	110·4		C(2A)—C(2)—N(3)	116·6
O(A1)—C(A1)—N(1)	123·3		O(2)—C(2)—N(3)	121·8
C(A1)—N(1)—C(1A)	124·1		C(2)—N(3)—C(3A)	119·3
C(A1)—N(1)—C(1D)	122·1		C(2)—N(3)—C(3D)	128·0
C(1A)—N(1)—C(1D)	113·7		C(3A)—N(3)—C(3D)	112·6
N(1)—C(1A)—C(1B)	102·5		N(3)—C(3A)—C(3B)	102·6
C(1A)—C(1B)—C(1C)	104·7		C(3A)—C(3B)—C(3C)	108·1
C(1B)—C(1C)—C(1D)	104·5		C(3B)—C(3C)—C(3D)	110·0
C(1C)—C(1D)—N(1)	102·6		C(3C)—C(3D)—N(3)	104·2
N(1)—C(1A)—C(1)	111·7		N(3)—C(3A)—C(3)	110·4
C(1B)—C(1A)—C(1)	109·8		C(3B)—C(3A)—C(3)	112·5
C(1A)—C(1)—O(1)	119·6		C(3A)—C(3)—O(31)	125·7
C(1A)—C(1)—N(2)	118·7		C(3A)—C(3)—O(32)	110·4
O(1)—C(1)—N(2)	121·7		O(31)—C(3)—O(32)	123·9
C(1)—N(2)—C(2A)	127·9		C(3)—O(32)—C(32)	116·6
C(1)—N(2)—C(2D)	121·1			

Table 3. *Conformational parameters*

Torsion angles (°) of the backbone. The range of the e.s.d.'s is 0·3–0·6° (mean 0·40°)

C(A32)—C(A2)—O(A2)—C(A1)	θ_2	176·9	C(1)—N(2)—C(2A)—C(2)	φ_2	−70·5
C(A2)—O(A2)—C(A1)—N(1)	θ_1	−168·7	N(2)—C(2A)—C(2)—N(3)	ψ_2	160·7
O(A2)—C(A1)—N(1)—C(1A)	ω_0	3·5	C(2A)—C(2)—N(3)—C(3A)	ω_2	−176·5
C(A1)—N(1)—C(1A)—C(1)	φ_1	58·3	C(2)—N(3)—C(3A)—C(3)	φ_3	70·4
N(1)—C(1A)—C(1)—N(2)	ψ_1	−138·1	N(3)—C(3A)—C(3)—O(32)	ψ_3	−163·6
C(1A)—C(1)—N(2)—C(2A)	ω_1	12·1	C(3A)—C(3)—O(32)—C(32)	ω_T	−178·8

Torsion angles (°) of the pyrrolidine rings. The range of the e.s.d.'s is 0·4–0·6° (mean 0·47°)

		D-Pro1	L-Pro2	D-Pro3
N—C$^\alpha$—C$^\beta$—C$^\gamma$	χ_1	24·1	29·8	−16·2
C$^\alpha$—C$^\beta$—C$^\gamma$—C$^\delta$	χ_2	−34·7	−39·1	13·4
C$^\beta$—C$^\gamma$—C$^\delta$—N	χ_3	31·1	32·8	−4·8
C$^\gamma$—C$^\delta$—N—C$^\alpha$	χ_4	−16·4	−14·3	−6·2
C$^\delta$—N—C$^\alpha$—C$^\beta$	χ_5	−4·5	−9·5	13·7

owing to the cyclic nature of the residue. Moreover, X-ray crystal structure analyses and conformational energy calculations show that the ψ angle of a proline residue, when another proline residue follows, is constrained within the ranges $129 \le \psi \le 191°$ and $-38 \le \psi \le -14°$ for L residues (Benedetti *et al.*, 1983). These allowed ranges of φ and ψ define, in the $\varphi-\psi$ Ramachandran plot, two regions, F and A, according to the one-letter code introduced by Zimmerman, Pottle, Némethy & Scheraga (1977). The F

$C_{21}H_{33}N_3O_6$

conformation is also called the collagen-type or polyproline II conformation, while the A region is that of the α-helical conformations. For the D residues the preceding values change sign and define the regions called F^* and A^*.

The structure of the title compound has been compared with those of the D,L-diproline and D,L,D,L-tetraproline methyl ester derivatives (Colapietro *et al.*, 1986) with which it forms a short series. The structure of the D,L-diproline derivative has been derived by inversion of the corresponding L,D enantiomer (Benedetti *et al.*, 1980). The results of this comparison are presented in Table 4 and in Fig. 2.

The sequence *trans-trans-cis* of the dihedral angles θ_2, θ_1 and ω_0, which determine the conformation of the *tert*-Boc group, is common to all three compounds and is that usually found when the protecting group is bonded to a tertiary nitrogen (Benedetti *et al.*, 1980). Also the conformation of the methyl ester C-terminal group is identical in all three molecules.

The di- and tetraproline derivatives show a high degree of conformational correspondence. In the backbone of the dimer the sequence F^*-*trans-F* is found, as in the tetramer where it is duplicated after a cis-peptide bond. Otherwise, in the tripeptide the sequence is F^*-*cis-F-trans-F*$ (Table 4). It gives a completely different shape to the structure of the trimer (Fig. 2). The conformational change occurring in the trimer is probably dictated by the need to retain at both terminal groups the local conformations, which are strictly invariant. It is apparently a paradox that the rough shape of this kind of polypeptide chain depends only on the *cis-trans* switch about the rigid peptide bond, whereas the rotational freedom around the single N—C^α and C^α—C' bonds is restricted to give a certain flexibility to the structures.

Pyrrolidine conformations

Pro1 shows a conformation almost exactly intermediate between C_s—C^γ-*exo* and C_2—C^γ-*exo*—C^β-*endo*, while Pro2 is a pure C_2—C^γ-*endo*—C^β-*exo*, according to the classification proposed by Ashida & Kakudo (1974). In terms of the notation scheme introduced by Balasubramanian, Lakshminarayanian, Sabesan, Tegoni, Venkatesan & Ramachandran (1971), these conformations belong to groups A and B respectively and lie in the range of those most commonly found in X-ray analyses, as can be seen by inspection of the summary compiled by De Tar & Luthra (1977). Pro3 shows a flat conformation not classifiable in terms of the previous notation. In this ring, the bond lengths C^β—C^γ and C^γ—C^δ appear to be anomalously short and the valence angle C^δ—C^γ—C^β anomalously large, while

Table 4. *Comparison of the backbone conformations of the di-, tri- and tetraproline compounds*

θ_2, θ_1 and ω_0 are the conformational parameters of the *tert*-Boc N terminus and are defined in Table 3 together with ω_T, the conformational parameter of the methyl ester C terminus.

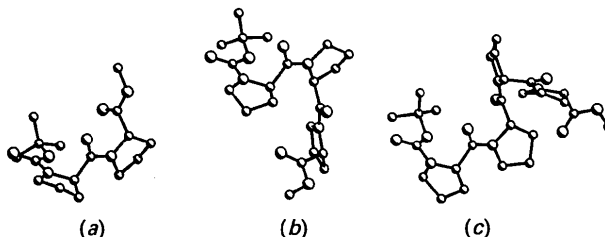|	Tetra	Tri	Di
θ_2	*trans*	*trans*	*trans*
θ_1	*trans*	*trans*	*trans*
ω_0	*cis*	*cis*	*cis*
φ_1/ψ_1	*F**	*F**	*F**
ω_1	*trans*	*cis*	*trans*
φ_2/ψ_2	*F*	*F*	*F*
ω_2	*cis*	*trans*	—
φ_3/ψ_3	*F**	*F**	—
ω_3	*trans*	—	—
φ_4/ψ_4	*F*	—	—
ω_T	*trans*	*trans*	*trans*

Fig. 2. The conformations found in the crystal structures of (a) D,L-diproline, (b) D,L,D-triproline and (c) D,L,D,L-tetraproline methyl ester, shown from a common point of view. For the sake of clarity, the H atoms are omitted.

the component of the thermal factor perpendicular to the plane of the pyrrolidine ring is particularly large for C^γ and C^β. This is not rare in pyrrolidine systems (Kartha, Ashida & Kakudo, 1974). All these findings are in accord with the common opinion which ascribes great flexibility to the pyrrolidine system.

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Structure of an Unusual Octacyclic Cage Compound

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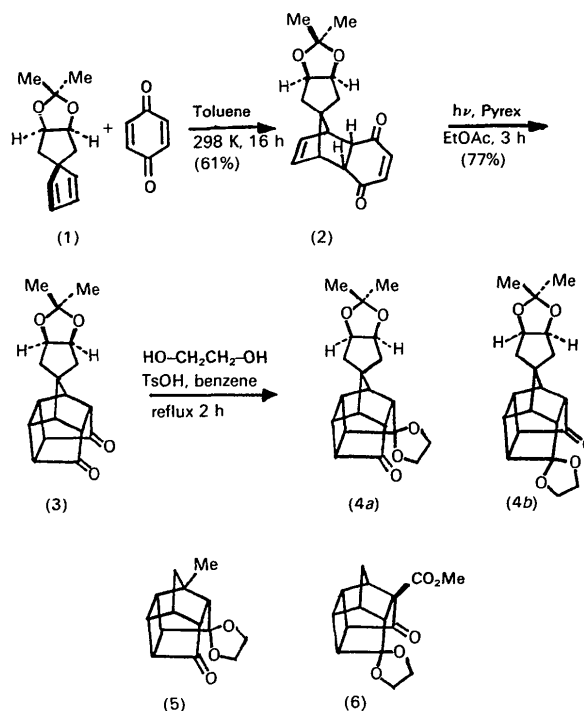AND ALAN P. MARCHAND* AND TENG-KO NGOOI

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Abstract. 11,11-Ethylenedioxypentacyclo[5.4.0.0^{2,6}.-0^{3,10}.0^{5,9}]undecane-4-spiro-7'-(*syn*-3',3'-dimethyl-2',4'-dioxabicyclo[3.3.0]octan)-8-one (4*a*), C$_{20}$H$_{24}$O$_5$, $M_r = 344.45$, monoclinic, $P2_1/c$, $a = 11.466$ (2), $b = 7.744$ (1), $c = 19.249$ (2) Å, $\beta = 98.85$ (1)°, $V = 1688.8$ (3) Å^3, $Z = 4$, $D_x = 1.360$ g cm^{-3}, λ(Mo Kα) = 0.71073 Å, $\mu = 1.00$ cm^{-1}, $F(000) = 736$, $T = 295$ K, $R = 0.0615$ for 2472 reflections. The molecule consists of a cage containing four five-membered rings and a four-membered ring. The cage is spiro fused to a *cis*-fused dioxabicyclooctane ring and to an ethylenedioxy moiety. One bond in the cage is lengthened to 1.568 (3) Å.

Introduction. In connection with an ongoing study of the synthesis and chemistry of novel, substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (PCUs; Marchand, 1989), the Diels–Alder cycloaddition of spirocyclic diene (1) (Semmelhack, Foos & Katz, 1973) to *p*-benzoquinone has been investigated. Thus, when an equimolar toluene solution of the diene and dienophile was stirred at ambient temperature for 16 h, the corresponding cycloadduct (2) was produced in 61% yield. The fact that this adduct possesses the *endo* configuration was demonstrated by its facile intramolecular [2 + 2] photocyclization to the corresponding substituted PCU, (3), in 77% yield. When a benzene solution of (3) and ethylene glycol (1 equivalent) containing a catalytic amount of *p*-toluenesulfonic acid was refluxed for 2 h (Eaton,

Cassar, Hudson & Hwang, 1976), a mixture of products was formed. Careful fractional recrystallization of the mixture from ethyl acetate afforded a single monoethylene ketal, C$_{20}$H$_{24}$O$_5$, m.p. 467–468 K. The structure of this compound is shown to be (4*a*) [rather than (4*b*)] *via* single-crystal X-ray structural analysis.