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A silaproline-containing dipeptide

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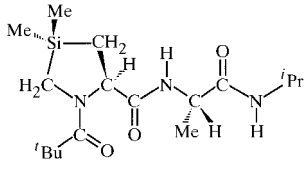
The silaproline-containing dipeptide *N*-(3,3-dimethyl-1-pivaloyl-1-aza-3-sila-5-cyclopentylcarbonyl)-L-alanine isopropylamide, $C_{17}H_{33}N_3O_3Si$, has two independent molecules in the asymmetric unit and each adopts a β-II folded conformation, where the amide on the terminal C interacts intramolecularly with the pivaloyl O atom. The five-membered silaproline ring is C^{β}-puckered, an infrequent conformation for the homologous proline ring.

Comment

Proline analogues are of great interest due to the importance of such a residue in peptide reverse-turn structures. Recently, we reported the synthesis of 4-(dimethylsila)-L-proline or silaproline (Sip) in both optically pure forms (Vivet *et al.*, 2000) by diastereoselective alkylation of a chiral glycine equivalent using Schöllkopf's bis-lactim ether method (Schöllkopf *et al.*, 1981). These Si-containing proline analogues may also be useful as solubilizing building blocks due to the high lipophilicity of silyl groups. This new proline surrogate has been introduced in model peptides in place of proline



(III)

to investigate the structural consequences of this modification. One of the targeted peptides, *N*-(3,3-dimethyl-1-pivaloyl-1-aza-3-sila-5-cyclopentylcarbonyl)-L-alanine isopropylamide, or Piv-L-Sip-L-Ala-NH^{i}Pr, (III), gave satisfactory single crystals for X-ray diffraction. We report here the first molecular crystal structure, to our knowledge, of a silaproline-containing peptide.

The dimensions of both independent molecules, *A* and *B*, in the monoclinic unit cell of (III) are quite similar. As expected, the Si—C bonds in the five-membered ring of the silaproline are longer by about 0.55 Å than the C—C bonds in proline, and the intracyclic C—Si—C angle is significantly smaller (about 92°) than the homologous C—C—C angle in proline (Table 1; Aubry, Vitoux & Marraud, 1985). The five-membered ring of silaproline assumes a skew conformation of the C^{β}-*endo* type (Nair & Vijayan, 1981), which is otherwise only found in the *cis*-proline residue involved in the 2,5-diketopiperazine ring (Aubry, Cung & Marraud, 1985).

Both independent molecules are folded by an intramolecular hydrogen bond between the amide on the terminal C and the pivaloyl O atom, which closes a ten-membered pseudocycle (Fig. 1). The orientation of the central amide group (Table 1) with reference to the average plane of the molecules is typical of a type II β-turn (Rose *et al.*, 1985). Although this turn type is not frequently found for homochiral dipeptide sequences in solution, it is classically observed in the crystal structures of similar dipeptides, due to favorable intermolecular packing forces involving the central amide NH and CO groups (Table 2; Aubry, Cung & Marraud, 1985). In solution, at a very low concentration in order to avoid autoassociation, the folded structure turns into a type I β-turn, as already observed in L-Pro-L-Xaa sequences by Aubry *et al.* (1985).

The crystal structure of (III) is composed of layers containing molecules *A* and layers containing molecules *B*, both oriented parallel to (100) (Fig. 2). In each layer, the molecules are stabilized by van der Waals interactions and the layers are held together by NH$\cdots$O hydrogen bonds (Table 2). Moreover, the independent molecules are connected by a non-crystallographic twofold screw axis which is in the crystallographic *a* direction and located at $y = 0.26$ (near $\frac{1}{4}$) and $z = 0.38$ (near $\frac{3}{8}$). The non-crystallographic operator, identified by the program *BUNYIP* (Hester & Hall, 1996), is $(\frac{1}{2} + x, \frac{1}{2} - y, \frac{3}{4} - z)$. Operation of the crystallographic twofold screw

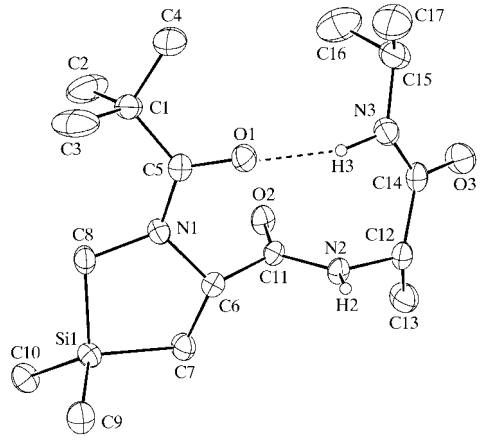


Figure 1
The molecular structure of the independent molecule *A* in (III) with the atom-numbering scheme and 25% probability displacement ellipsoids. H atoms, except for those of the NH groups, have been omitted for clarity. The intramolecular hydrogen bond is marked as a dashed line.

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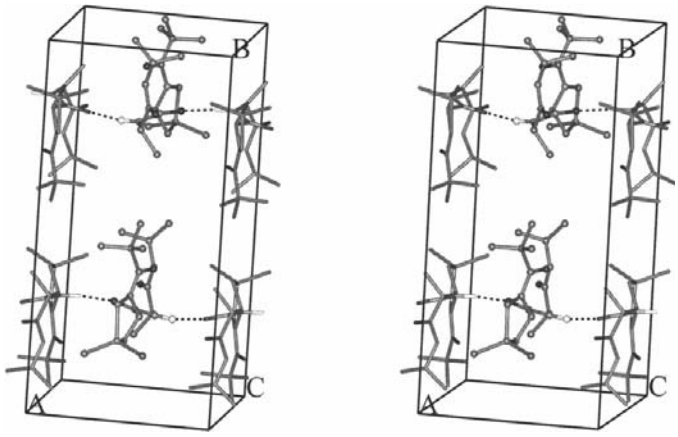

Figure 2
A stereoview of the crystal structure of (III), which is composed of alternating layers of *A* (stick representation) and *B* molecules (ball and stick representation), oriented parallel to (100). The intermolecular hydrogen bonds are marked as dashed lines. H atoms, except those of the NH groups involved in the intermolecular interactions, have been omitted for clarity.

symmetry on the non-crystallographic twofold screw axis yields a second non-crystallographic twofold screw axis in the same direction and associated with the operator $(\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{4}-z)$. It is interesting to note that both non-crystallographic axes extend throughout the crystal, since their self-operation yields (x, y, z). Combinations of the non- and the true crystallographic axes result in two more non-crystallographic twofold screw axes, which present the operators $(\frac{1}{2}-x, -y, \frac{1}{4}+z)$ and $(\frac{1}{2}-x, -y, \frac{3}{4}+z)$. These twofold screw axes do not extend througout the crystal, because their self-operation does not yield (x, y, z) or any other symmetry element.

Experimental

N-(*tert*-Butyloxycarbonyl)-L-alanine (Boc-L-Ala-OH) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) were purchased from Novabiochem, and diisopropylethylamine (DIEA), isopropylamine and pivaloyl chloride (PivCl) from Aldrich. Dichloromethane (DCM) was dried overnight over $CaCl_2$, then distilled over K_2CO_3 and stored away from bright light in a brown bottle. Dimethylformamide (DMF), acetonitrile and trifluoroacetic acid (TFA) were purchased from Merck. Thin-layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates and spots were visualized by staining with phosphomolybdic acid or ninhydrin. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). To prepare Boc-L-Ala-NH^{i}Pr, (I), Boc-L-Ala-OH (350 mg, 1.85 mmol) was dissolved in DMF (5 ml) and then BOP (900 mg, 2.40 mmol), isopropylamine (170 µl, 2 mmol) and DIEA (785 µl, 4.62 mmol) were added. After 4 h at room temperature, the reaction mixture was evaporated *in vacuo* and the resulting residue dissolved in EtOAc (15 ml). The organic phase was washed successively with aqueous 0.1 *N* $KHSO_4$ (3 × 5 ml) and saturated $NaHCO_3$ (3 × 5 ml), dried over $MgSO_4$ and then concentrated *in vacuo*. The crude product was purified by chromatography on silica gel in EtOAc/hexane (6:4) to give 360 mg of (I) (85% yield) as an oil; R_f = 0.30 (EtOAc/hexane 6:4) and R_f = 0.55 (EtOAc/hexane 7:3). To prepare Boc-L-Sip-L-Ala-NH^{i}Pr, (II), a solution of (I) (250 mg, 1.08 mmol) in DCM (3 ml) was stirred for 1 h at room temperature with TFA (3 ml). The mixture was evaporated *in vacuo* and the residue was coevaporated three times with hexane/Et_2O 4:2 (10 ml) to remove excess TFA. The TFA salt (260 mg, 1.06 mmol) was dissolved in DMF (5 ml). DIEA (450 µl, 2.65 mmol), BOP (514 mg, 1.16 mmol) and Boc-L-Sip-OH (Vivet *et al.*, 2000) (275 mg, 1.06 mmol) were then added. After stirring overnight at room temperature, the reaction mixture was evaporated *in vacuo* and the resulting residue dissolved in EtOAc (15 ml). The organic phase was washed successively with aqueous 0.1 *N* $KHSO_4$ (3 × 5 ml) and saturated $NaHCO_3$ (3 × 5 ml), dried over $MgSO_4$ and then concentrated *in vacuo*. The crude product was purified by chromatography on silica gel in EtOAc/hexane 6:4, to give 300 mg of (II) (76% yield) as an oil; R_f = 0.40 (EtOAc/hexane 6:4). To prepare Piv-L-Sip-L-Ala-NH^{i}Pr, (III), a solution of (II) (250 mg, 0.67 mmol) in DCM (3 ml) was stirred for 1 h at room temperature with TFA (3 ml). The mixture was evaporated *in vacuo* and the residue was coevaporated three times with hexane/Et_2O 4:2 (10 ml) to remove excess TFA. The TFA salt (240 mg, 0.62 mmol) was dissolved in DCM (5 ml). DIEA (210 µl, 1.24 mmol) and PivCl (85 µl, 0.68 mmol) were then added. After stirring overnight at room temperature, the reaction mixture was evaporated *in vacuo* and the resulting residue dissolved in EtOAc (15 ml). The organic phase was washed successively with aqueous 0.1 *N* $KHSO_4$ (3 × 5 ml) and saturated $NaHCO_3$ (3 × 5 ml), dried over $MgSO_4$ and then concentrated *in vacuo*. The crude product was purified by chromatography on silica gel in EtOAc/hexane 6:4, to give 154 mg of (III) (70% yield) as a solid; R_f = 0.50 (EtOAc/hexane 6:4). Single crystals of (III) were obtained at room temperature by slow evaporation of a solution in a mixture of diisopropyl ether and ethyl acetate.

Crystal data

$C_{17}H_{33}N_3O_3Si$	D_x = 1.117 Mg m^{-3}
M_r = 355.55	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 9566 reflections
a = 9.6650 (5) Å	θ = 2.1–25.0°
b = 19.6620 (9) Å	μ = 0.129 mm^{-1}
c = 11.123 (2) Å	T = 293 (2) K
β = 89.602 (5)°	Prismatic, colourless
V = 2113.7 (4) Å^3	0.3 × 0.2 × 0.2 mm
Z = 4	

Data collection

Nonius KappaCCD diffractometer	R_{int} = 0.055
Oscillation scans	θ_{max} = 25°
9566 measured reflections	$h = -10 \rightarrow 10$
3659 independent reflections	$k = -23 \rightarrow 23$
3090 reflections with $I > 2\sigma(I)$	$l = -13 \rightarrow 13$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0749P)^2 + 0.8441P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.055	$(\Delta/\sigma)_{max}$ = 0.001
$wR(F^2)$ = 0.143	$\Delta\rho_{max}$ = 0.23 e Å^{-3}
S = 1.072	$\Delta\rho_{min}$ = −0.22 e Å^{-3}
3659 reflections	
445 parameters	
H atoms treated by a mixture of independent and constrained refinement	

The atom-numbering schemes chosen for the independent molecules *A* and *B* are in the ranges 1–17 and 21–37, respectively. The absolute stereochemistry of the L-Sip derivative was confirmed on the basis of the L-Ala residue. The positions of H atoms attached to N atoms were located from a difference map and refined with the N—H bond distance restrained to 1.03 (1) Å (Taylor & Kennard, 1983). H atoms connected to C atoms were placed at calculated positions and refined using a riding model (C—H 0.96–0.97 Å). All H atoms had

Table 1
Selected geometric parameters (Å, °).

N1—C6	1.462 (7)	N21—C26	1.483 (6)
N1—C8	1.497 (6)	N21—C28	1.488 (6)
C6—C7	1.525 (7)	C26—C27	1.532 (7)
Si1—C7	1.877 (6)	Si21—C27	1.879 (6)
Si1—C8	1.872 (6)	Si21—C28	1.890 (6)
Si1—C9	1.868 (6)	Si21—C29	1.852 (5)
Si1—C10	1.854 (5)	Si21—C30	1.848 (6)
C6—N1—C8	114.8 (4)	C26—N21—C28	117.3 (4)
N1—C6—C7	111.1 (4)	N21—C26—C27	108.3 (4)
C6—C7—Si1	104.5 (3)	C26—C27—Si21	105.8 (3)
N1—C8—Si1	106.8 (4)	N21—C28—Si21	105.7 (3)
C7—Si1—C8	92.9 (2)	C27—Si21—C28	92.1 (2)
C7—Si1—C9	112.7 (3)	C27—Si21—C29	113.8 (3)
C7—Si1—C10	113.6 (3)	C27—Si21—C30	113.7 (3)
C8—Si1—C9	113.1 (3)	C28—Si21—C29	111.8 (3)
C8—Si1—C10	112.9 (3)	C28—Si21—C30	112.4 (3)
C9—Si1—C10	110.7 (3)	C29—Si21—C30	111.7 (3)
C5—N1—C6—C11	−49.5 (6)	C25—N21—C26—C31	−51.2 (5)
N1—C6—C11—N2	136.5 (4)	N21—C26—C31—N22	137.9 (5)
C11—N2—C12—C14	63.3 (6)	C31—N22—C32—C34	63.5 (6)
N2—C12—C14—N3	20.1 (6)	N22—C32—C34—N23	20.9 (6)
N1—C6—C7—Si1	−33.1 (5)	N21—C26—C27—Si21	−33.8 (5)
C6—C7—Si1—C8	24.9 (4)	C26—C27—Si21—C28	28.3 (4)
C7—Si1—C8—N1	−11.3 (4)	C27—Si21—C28—N21	−15.0 (4)
Si1—C8—N1—C6	−6.6 (5)	Si21—C28—N21—C26	−2.9 (5)

their isotropic displacement parameters fixed at 1.3 times that of the parent atom.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *COLLECT* (Nonius, 1998); data reduction: *HKL* suite (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *maXus* (Mackay *et al.*, 1999) and *WebLab ViewerPro* 3.5 (MSI, 1999).

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O22^{i}	1.03 (2)	1.81 (2)	2.831 (5)	172 (5)
N23—H23···O21	1.03 (2)	2.13 (2)	3.122 (6)	166 (5)
N3—H3···O1	1.03 (2)	2.12 (2)	3.118 (6)	163 (5)
N22—H22···O2	1.02 (2)	1.83 (2)	2.847 (5)	169 (5)

Symmetry code: (i) $x-1, y, z$.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1107). Services for accessing these data are described at the back of the journal.

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