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Conformational studies of proline-, thiaproline- and dimethylsilaproline-containing diketopiperazines

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Abstract: As proline plays an important role in biologically active peptides, many analogues of this residue have been developed to modulate the proportion of *cis* and *trans* conformers. A correlation between the pyrrolidine ring shape and structural properties of proline has been established. Diketopiperazine (DKP) is the model of choice to study the influence of the proline ring modification. In this contribution, cyclo(Gly-Pro) and two analogues cyclo(Sip-Pro) and cyclo(Thz-Pro) have been studied with proton NMR. We showed that both analogues with heteroatoms in γ position, silicon and sulfur respectively, display a more rigid five-member ring. The usual flexibility of proline ring is restrained in both cases and only the two C^{β}-exo and C^{β}-endo conformations are observed.

Keywords: proline; dimethylsilaproline; thiaproline; diketopiperazine; thiazolidine-4-carboxylic acid; proton NMR

INTRODUCTION

Among all essential amino acids, proline is the only natural cyclic residue. The bulky pyrrolidine ring restricts the local conformation freedom, leading to altered molecular flexibility and lowering the number of possible conformers. In addition, proline is well known for its ability to undergo *cis*/*trans* isomerisation and form *cis* peptide bonds that can induce type VI β-turns. Indeed, the isomerisation barrier of peptide bonds in proline-containing molecules is lowered owing to concomitant pyrrolidine puckering changes, favouring the existence of the *cis*-population compared to other peptide bonds. Owing to these unique properties, proline plays an important role in biological processes and biologically active peptides. Therefore, replacement of proline with substituted analogues often results in introduction of rigidity into bioactive peptides, and may provide information about receptor recognition and affinity. Accordingly, numerous surrogates, mimetics and analogues of proline were developed. The first class is constrained analogues, which are designed with the aim of governing the *cis*/*trans* ratio of proline peptide bonds. The second class is non-constrained analogues, which are supposed to conserve the native properties of proline. A typical example of hindered substituted proline is offered by Lubell [1,2], who described δ-*tert*-butylproline to constrain the tridimentional conformation of peptides and to produce proline-like turns. In the second category, pseudoproline residues [3] were investigated to circumvent solubility problems correlated with hydrophilic side chains.

The *cis*/*trans* isomerisation of the proline peptide bond has been studied extensively and depends on several factors such as solvent [4], aromaticity [5] or chirality [6] of the residue preceding the proline, or additional constraints imposed by a disulfide bond [7]. To modulate the proportion of *cis* and *trans* conformers, C^{β}-substitution has the advantage of orienting the substituent in a given direction depending on their *cis* or *trans* stereochemistry [8–11]. δ-Substituted proline, like δ-*tert*-butylproline [1,2] and δ,δ-dimethylproline [12], have been developed as substitutes to lock the *cis*-proline conformation into peptides. However, modification of the γ-position has been mentioned to minimally interact with the proline conformation [13–15]. In this important field of modified prolines, we recently reported the synthesis of a new silicon-containing proline surrogate, the γ-(dimethylsila)-proline, denoted Sip [16]. The presence of the dimethylsilyl group is expected to promote higher lipophilicity, as proven by the octanol-water coefficient of Sip, which was experimentally determined to be 14 times greater than that for Pro. Increased lipophilicity may therefore facilitate membrane permeability. Moreover, analogous Sip- and Pro-containing model peptides exhibited similar conformational properties, ascertained by IR absorption and NMR techniques [17]. Incorporation of silaproline in replacement of proline into neurotensin(8–13) [17] and substance P [18] resulted in analogues with retention of receptor affinity, *in vivo* bioactivity and improved resistance to enzymatic degradation, thus highlighting the interest of such analogues.

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Another problem with proline analogues is related to the five-member ring conformation, which is fluctuant in proline, and often constrained in substituted analogues. We know that a correlation between ring shape and structural properties of proline exists, especially owing to the ϕ angle. In silaproline, we showed that this ring adopts two forms: C^{β}-endo in Piv-Sip-Ala-NHiPr in the solid state (only present for proline in (Pro-Xxx)DKP) and C^{β}-exo in several Sip derivatives in solution. To study the ring shape in Sip and Thz (thiazolidine-4-carboxylic acid), very similar to proline in terms of structure, we considered a rigid skeleton in which the only authorised fluctuation was in the thiaproline ring. We though that diketopiperazine (DKP) was a good model although the DKP cycle can possibly adopt flat, boat or twisted forms. Indeed DKPs of Pro-Xxx type where Xxx is Gly or a D-residue adopt a rigid boat shape in both solid state and solution. In this study, we report the conformational study of (Gly-Pro), (Gly-Thz) and (Gly-Sip) DKPs.

RESULTS AND DISCUSSION

Bicyclic dipeptides (Xxx-L-Pro) and (Xxx-D-Pro) have been previously synthesised to force the *cis* amide conformation [19] (Figure 1(A)) or the *trans* amide conformation [20] (Figure 1(B)).

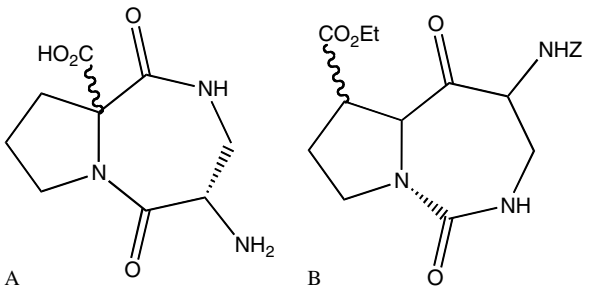

Figure 1 Bicyclic dipeptides having a constrained *cis*-proline amide bond (A) or a *trans*-proline amide bond (B).

DKP is a model of choice to study the influence of the proline ring modification since the resulting bicyclic dipeptides are synthesised in a straightforward manner, particularly constrained and easy to analyse by proton NMR [21,22]. We chose to synthesise the cyclo(Gly-Pro) dipeptide to avoid influence of side chain (Figure 2).

Techniques and Correlations Used to Described DKP Structures

The boat-shaped DKP ring suits a particular position of NH–$C^{\alpha}H_2$ fragment, with two HN–CH and HN–CH′ dihedral angles of about 30° and 90° respectively, leading to two different H_N/H et H_N/H′ couplings, one (H_N/H) being very low (<1 Hz) and the second (H_N/H′), middle range (4–5 Hz) [23].

Like proline [23], thiaproline rings may fluctuate between 4 limit envelope forms (Figure 3). Atoms in the β or γ position may be above or below the plane defined by the four others atoms. These forms are characterised by a set of two dihedral angles in the $C^{\alpha}H$–$C^{\beta}H_2$ system: around 30° ($H^{\alpha}C^{\alpha}$–$C^{\beta}H^{\beta}{}_c$) and 90° ($H^{\alpha}C^{\alpha}$–$C^{\beta}H^{\beta}{}_t$) in both C^{β}-exo and X^{γ}-endo conformations, and about 30° ($H^{\alpha}C^{\alpha}$–$C^{\beta}H^{\beta}{}_c$) and 150° ($H^{\alpha}C^{\alpha}$–$C^{\beta}H^{\beta}{}_t$) in both C^{β}-endo and X^{γ}-exo conformations. The dihedral angle of 30° corresponds to a medium coupling (6–9 Hz), of 90° to a small coupling (2–4 Hz), and of 150° to a large coupling (10–15 Hz) [23]. Therefore, a set of two medium couplings should be explained by a rapid equilibrium between two forms, with the $H^{\alpha}C^{\alpha}$–$C^{\beta}H^{\beta}{}_c$ dihedral angle of about +30° or −30° (2 medium couplings leading to a medium mean) and the $H^{\alpha}C^{\alpha}$–$C^{\beta}H^{\beta}{}_t$ dihedral angle of about 90° or 150° (a smaller and a larger couplings leading also to a medium mean) (Figure 3).

The Pro, Thz and Sip spin systems have been delineated by COSY experiments. The coupling constants for Thz and Sip have been directly measured on $C^{\beta}H_2$ and $C^{\delta}H_2$ signals. The same coupling constants for Pro have been obtained by specific irradiation of the Pro-$C^{\beta}H_2$ and $C^{\gamma}H_2$ protons. The main H^1-NMR data of interest are listed in Table 1. The diastereoscopic $C^{\beta}H_2$ protons have been assigned because of the following

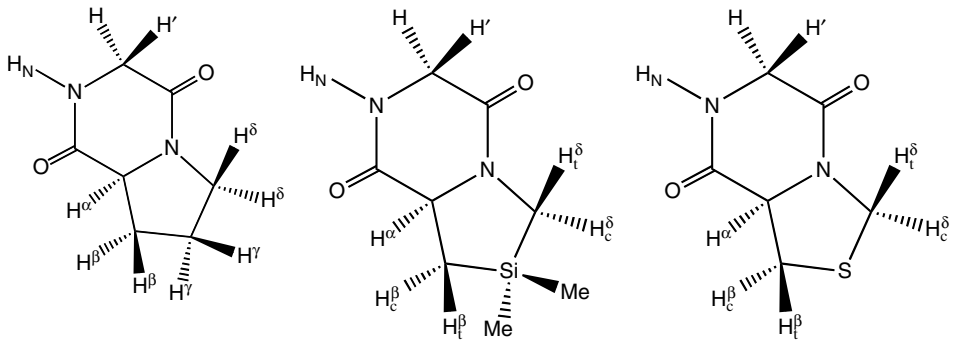

Figure 2 Structures of the diketopiperazines studied.

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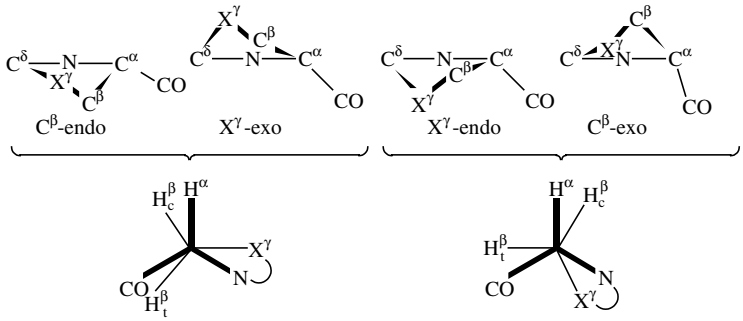

Figure 3 The four possible envelope conformations of the Pro ($X^{\gamma} = C$), Sip ($X^{\gamma} = Si(Me)_2$) or Thz ($X^{\gamma} = S$) ring with the relative orientation of the vicinal protons in $C^{\alpha}H–C^{\beta}$]. The *cis* or *trans* orientation of the $C^{\beta}H_2$ protons is defined with reference to H^{α}.

Table 1 NMR Data for the analogous Sip-, Thz- and Pro-containing DKPs

				(Sip-Gly) DKP				
δ (ppm)	H_N	H	H′	H^{α}	$H^{\beta}{}_c$	$H^{\beta}{}_t$	$H^{\delta}{}_t/H^{\delta}{}_c$	Me
	7.32	3.83	3.58	4.08	1.24	0.96	2.98/2.36	0.18/0.19
J(Hz)	H_NH	H_NH'	HH′	$H^{\alpha}H^{\beta}{}_c$	$H^{\alpha}H^{\beta}{}_t$	$H^{\beta}{}_tH^{\beta}{}_c$	$H^{\delta}{}_tH^{\delta}{}_c$	—
	0.8	4.6	−22.7	9.2[a]	15.4[a]	−19.5[a]	−20.6	—
				(Thz-Gly) DKP				
δ (ppm)	H_N	H	H′	H^{α}	$H^{\beta}{}_c$	$H^{\beta}{}_t$	$H^{\delta}{}_t/H^{\delta}{}_c$	—
	—	4.05	3.67	4.39	3.32	3.17	4.78/4.33	—
J(Hz)	H_NH	H_NH'	HH′	$H^{\alpha}H^{\beta}{}_c$	$H^{\alpha}H^{\beta}{}_t$	$H^{\beta}{}_tH^{\beta}{}_c$	$H^{\delta}{}_tH^{\delta}{}_c$	—
	1.0	5.2	−22.7	8.8[b]	11.8[b]	−15.1[b]	−12.8	—
				(Pro-Gly) DKP				
δ (ppm)	H_N	H	H′	H^{α}	$H^{\beta}{}_t$	$H^{\beta}{}_c$	$H^{\gamma}{}_t/H^{\gamma}{}_c$	$H^{\delta}{}_t/H^{\delta}{}_c$
	8.05	3.98	3.50	4.12	2.12	1.82	1.82	3.40/3.32
J(Hz)	H_NH	H_NH'	HH′	$H^{\alpha}H^{\beta}{}_c$	$H^{\alpha}H^{\beta}{}_t$	$H^{\beta}{}_tH^{\beta}{}_c$	$H^{\delta}{}_tH^{\delta}{}_c$	—
	1.0	4.6	−16.4	7.1[c]	5.6[c]	nd	−10.3[c]	—

[a] measured on $C^{\beta}H_2$ signals.
[b] measured on $C^{\beta}H_2$ signals.
[c] measured on H^{α} or H^{δ} signal after selective irradiation of $H^{\beta}{}_t$ or $H^{\beta}{}_c$.

reasons: (i) in a set of one large (>9 Hz) and one medium (7–9 Hz) $H^{\alpha}H^{\beta}$ coupling, the largest value was assigned to $H^{\beta}{}_t$ with a large $H^{\alpha}C^{\alpha}–C^{\beta}H^{\beta}{}_t$ dihedral angle; (ii) in a set of one medium (7–9 Hz) and one small (<4 Hz) $H^{\alpha}H^{\beta}$ coupling, the smaller value was assigned to $H^{\beta}{}_t$ with a $H^{\alpha}C^{\alpha}–C^{\beta}H^{\beta}{}_t$ dihedral angle of about 90°; and (iii) the higher coupling in a set of two medium $H^{\alpha}H^{\beta}$ coupling constants (4–9 Hz) was assigned to $H^{\beta}{}_c$ [24]. Of course, the nature of the γ-atom affected the local dimensions, and its electronegativity had a direct influence on the coupling constants [24]. For a given conformation of the five-membered pyrrolidine ring, the very low electronegativity of silicon in the Sip residue is expected to result in higher $H^{\alpha}H^{\beta}$ coupling than for sulfur in the Thz residue, and carbon in the Pro residue. The present attribution agrees with that already reported for (Thz-Gly)DKP in ^2H_2O and DMSO-d_6 [13].

Regarding the DKP moiety, these three molecules present some similarities, according to NMR data (Table 1). Coupling constants between H_N/H and H_N/H′ (1 Hz and 4.6–5.2 Hz respectively) showed that the DKP ring adopts a boat conformation with dihedral angles $H_N–N–C–H/H'$ of about 95° and 25° [25]. This conformation is commonly found in crystal structures of (Xxx-Pro)DKP, particularly cyclo(Gly-Pro) [26] and cyclo(Gly-Thz) [13]. For the latter compound, nearly the same conformation was proven in solution by the vicinal proton–proton coupling constants [13].

We were particularly interested in the modification induced on the pyrrolidine ring. We know from RX data [27] that some specificity is due to the silicon atom: long carbon–silicon bonds and small carbon–silicon–carbon intracyclic angle. Similar remarks are relevant with the sulfur atom [13]. The resulting envelope conformation is of the Cβ-endo type, in both cases (Si and S), in the solid state. It is characterised by a large $H^{\alpha}C^{\alpha}–C^{\beta}H^{\beta}{}_t$ dihedral angle (∼150°), and a small $H^{\alpha}C^{\alpha}–C^{\beta}H^{\beta}{}_c$ dihedral angle (∼30°). In proton NMR solution, based on the set of one medium (9.9–10.6 Hz) and one small (1.8–2.5 Hz) $H^{\alpha}C^{\alpha}–C^{\beta}H^{\beta}$ coupling constant, the linear Sip-containing peptides investigated so far did not retain the Cβ-endo puckering mode, but rather the

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Cβ-exo puckering mode [17]. The question was now to determine if the presence of the constrained DKP affected the puckering mode assumed by the Sip or Thz five-membered ring.

Comparing the 3 compounds previously described, we could observe fairly different sets of $H^{\alpha}C^{\alpha}-C^{\beta}H^{\beta}{}_{t}$ and $H^{\alpha}C^{\alpha}-C^{\beta}H^{\beta}{}_{c}$ couplings in (Gly-Pro)DKP on the one hand, and (Gly-Sip)DKP and (Gly-Thz)DKP on the other hand. While (Gly-Pro)DKP exhibited two medium coupling constants (5.6 and 7.1 Hz), the other two compounds displayed one large $H^{\alpha}C^{\alpha}-C^{\beta}H^{\beta}{}_{t}$ coupling constant (11.8 and 15.4 Hz respectively) and a medium $H^{\alpha}C^{\alpha}-C^{\beta}H^{\beta}{}_{c}$ coupling constant (8.8 and 9.2 Hz respectively). This suggests different conformations for the proline-like ring.

In the case of (Gly-Pro)DKP, the similar range of both couplings indicated an authorised ring flexibility between various forms (Figure 4) allowing a small ϕ angle imposed by the DKP ring closure. The most probable forms are the C^{β}-endo form (one medium and one high coupling constant), which was observed in the solid state for various (Xxx-Pro)DKPs, and the C^{γ}-endo form (one medium and one low coupling constant). Averaging the high and low values for the $H^{\alpha}C^{\alpha}-C^{\beta}H^{\beta}{}_{t}$ coupling constant may also give a medium coupling value.

When the γ-methylene group was substituted, the coupling pattern in the $H^{\alpha}C^{\alpha}-C^{\beta}H^{\beta}{}_{2}$ fragment (one high and one medium coupling value) indicated a very rigid conformation of the pyrrolidine-like five-membered ring, with the dihedral angle $H^{\alpha}C^{\alpha}-C^{\beta}H^{\beta}{}_{t}$ close to 150°, and the dihedral angle $H^{\alpha}C^{\alpha}-C^{\beta}H^{\beta}{}_{c}$ close to 30°. Considering the boat conformation of the DKP ring, the only possibility for the pyrrolidine ring was to adopt a C^{β}-endo envelope form. Among the two C^{β}-endo and X^{γ}-exo conformations theoretically possible on the basis of the NMR data, straightforward modelling calculations converge toward the former solution, the most thermodynamically stable one for (Gly-Sip)DKP and (Gly-Thz)DKP (Figure 5).

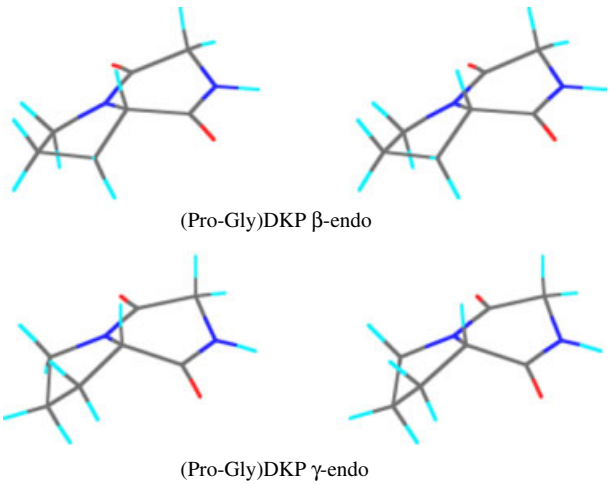

Figure 4 The two exchangeable conformations of (Gly-Pro)DKP, minimised with Chem Pro (stereo view).

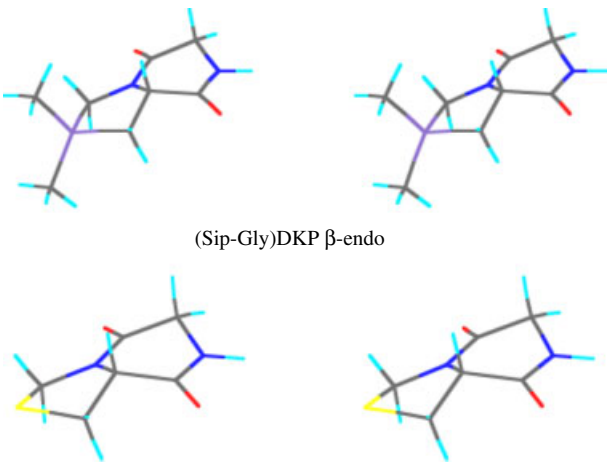

Figure 5 The calculated conformations of (Gly-Sip)DKP and (Gly-Thz)DKP (stereo view).

CONCLUSION

The results of this study highlight the rigidity of the Sip ring since we only observed the two C^{β}-exo and C^{β}-endo conformations, in both linear and cyclic compounds. The Si^{γ} atom still stands in the $C^{\delta}-N-C^{\alpha}$ plane. This makes a major difference with proline, in which flexibility is mainly due to the Cγ atom. Without any constraint, this C^{γ} atom quickly exchanges between endo and exo positions outside the $C^{\delta}-N-C^{\alpha}-C^{\beta}$ plane. To move the C^{β} atom away from the plane, a constraint is required: either a low ϕ angle in DKP ring ($\rightarrow C^{\beta}$-endo), or a large ϕ angle as in a β-folded form in which Pro occupies a i + 2 position ($\rightarrow C^{\beta}$-exo) [23]. In addition, the two methylene groups load the γ position, resulting in an increased inertia of the γ-position under thermal agitation. This is confirmed in the crystal structure of Piv-Sip-Ala-NHiPr where the Sip ring is only slightly agitated. This difference can be mainly attributed to geometry changes of the five-member ring, with longer bonds ($C^{\beta}-X^{\gamma}$ and $X^{\gamma}-C^{\delta}$) and smaller valence angle $C^{\beta}-X^{\gamma}-C^{\delta}$. The inertia due to the two methylene groups does not seem to be of primary importance since sulphur in (Thz-Gly)DKP has practically the same conformational influence as the dimethylsilyl group in (Sip-Gly)DKP.

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