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A Selection of Papers Presented at the Fall Meeting of the New Swiss Chemical Society (NSCS) in Lausanne, October 15, 1997

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Extending the Proline Effect: ΨPro for Tailoring *cis-trans* Isomerisation[a])

Pascal Dumy*

Abstract. Pseudo-Prolines (ΨPro) consist of (4*S*)-oxazolidine- and (4*R*)-thiazolidine-carboxylic acids derived from amino acids Ser, Thr and Cys. They represent new branched proline analogues in which variation of the substituents (R^1, R^2, R^3) results in different physicochemical and conformational properties. We summarise here the relevant chemical and structural aspects of such super-prolines intended to constrain and control the peptide backbone in β-turn motifs or to alter the imide *cis-trans* ratio.

Introduction

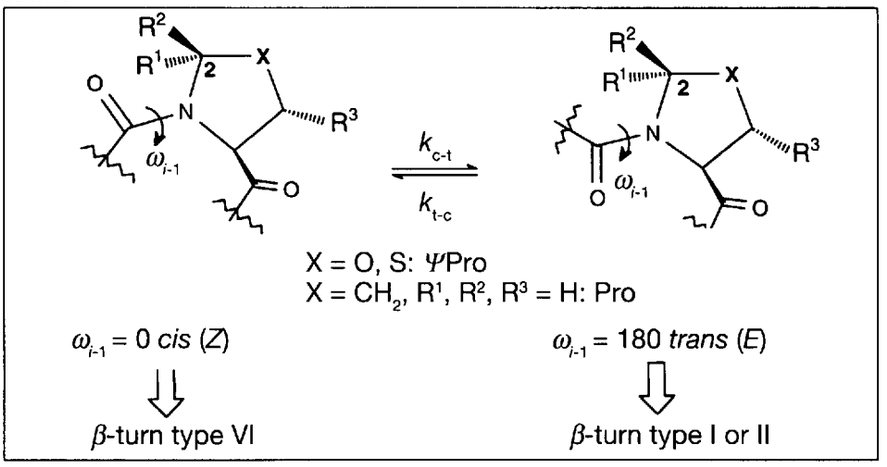
The proline residues play a critical role in peptide and protein structures and are usually encountered in loop or β-turn type I or type II (ω_i = 180°) or at the (*i*+2)-position of turn type VI (ω_{i+1} = 0°) [1][2] (*Scheme*; X = CH_2, R^1 = R^2 = R^3 = H). In this context, the prevalence of proline residues in biological processes such as protein folding and protein recognition [3a–d] has led to the development of numerous mimetics and substituted proline analogues intended to constrain and control the peptide backbone in reverse turn motifs or to alter the imide *cis-trans* ratio [4a–d].

Due to their structural similarities with proline and their easy synthetic availability, ΨPro (*Scheme*; X = O, S) represent potential surrogates to constrain the backbone or to tailor the *cis*-to-*trans* ratio in peptides, thus offering an important tool for studying the relationship between isomer geometry and peptide bioactivity.

Synthesis and Chemical Stabilities

ΨPro are generally incorporated into peptide backbones as dipeptide building blocks [5]. Oxazolidine ring formation is usually performed by reacting ketals directly on *N*-protected dipeptides containing Ser or Thr at the C-termini [6]. In contrast, thiazolidines can be obtained from cysteine and aldehydes or ketones and then incorporated within dipeptide units. The convenient preparation of these building blocks allows the introduction of various substituents at the 2-position which results in different physicochemical properties. For instance, the ring-chemical stability toward acids depends largely on the nature of the 2-position substituents, and, thus, ΨPro have been introduced as alter-

Scheme



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[a]) These results were presented as an oral presentation at the Autumn Meeting of the New Swiss Chemical Society (NSCS) in Lausanne, Switzerland, on October 15, 1997.

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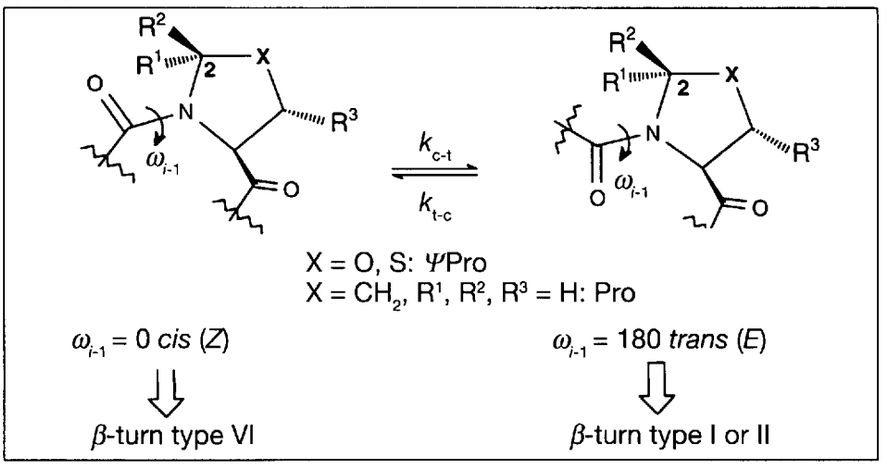

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native temporary protecting groups for the parent residues. Furthermore, this incorporation of this proline-like system disrupts intermolecular aggregation formations during solid-phase peptide assembly and then improve the efficiency of the synthesis [5].

Conformational Properties

We have determined by dynamic 2D-NMR and chymotrypsin-coupled assays the thermodynamic and kinetic parameters pertaining to the *cis-trans* isomerisation about the Xaa-ΨPro imidic bond (*Table*) in order to delineate the influence of the steric bulk and configuration of the 2-position substituents (R^1, R^2) on model peptides [7][8].

Thermodynamic

Unsubstituted and (2 *R*) systems show a strong thermodynamic preference for the *trans*-form similar to that of the proline residue in solution. For the (2 *S*)-substituted ΨPro epimers, both forms are similarly populated, whereas 2,2-dimethyl derivatives adopt the *cis*-amide geometry in an unusual high content (>90%) [8]. Steric interactions involving the 2-position substituents and the preceding residue provide some rational for the *cis-trans* ratio found in ΨPro-containing peptides. The interactions between the ring substituents and the preceding residue are maximised when the peptide bond is *trans*, and, consequently, the net free-energy difference between the *cis*- and *trans*-conformers increases so that the *cis*-form is principally observed for 2,2-dimethyl derivatives. This is supported by crystallographic data of thiazolidine derivatives which reveal the *cis*-geometry only for the 2,2-dimethyl substitution. It appears that the steric hindrance of the *trans*-form is the major driving force for adapting high *cis*-content. Beside steric effects, stereoelectronic effects play also a role in the isomerisation as demonstrated by *Hammett* correlations of 2-arylthiazolidines for the *cis-trans* ratio.

Kinetic

All the ΨPro-containing peptides displayed characteristic lowering of the isomerisation barriers compared to proline peptide (*Table*). Interestingly, the *trans*-to-*cis* barriers appear to be specifically affected with the 2-position substituents in a pattern following the thermodynamic preference for the *cis*-form (*i.e.*, $\Delta G^{\#(2,2\text{-Me}_2)}_{t-c} < \Delta G^{\#(2S)}_{t-c} < \Delta G^{\#(2R)}_{t-c}$). It is worth to notice that this decreases correlate perfectly with the CO–N bond-length values extracted from crystallographic data (l_{pro} = 1.345 Å < $l_{(2R)} \approx l_{(2S)}$ = 1.36 Å < $l_{Me,Me}$ = 1.39 Å). Again the largest effects on the $\Delta G^{\#}_{t-c}$, compared with the proline peptide, are obtained for 2,2-dimethyloxazolidines and -thiazolidines with values of 3.4 and 5.8 kcal/mol, respectively.

Table. *Thermodynamic and Kinetic Parameters Determined in H_2O for Peptides Succ-Val-ΨPro-Phe-PNa*

R^1, R^2	X	$\Delta G^{\#}_{c-t}$	$\Delta G^{\#}_{t-c}$	*cis*[%]	ΔG°_{c-t}
H, H	O	16.7	17.77	13	–1.09
Me, Me	O	18.9	17.90	85	1.00
Me, Me	S	18.3	15.50	99	2.70
(2*S*)pmp[a])	O	18.6	19.00	37	–0.32
(2*R*)pmp[a])	O	18.7	20.80	3	–2.06
(2*S*)pmp[a])	S	19.1	19.41	37	–0.32
H, H	CH_2	19.5	21.29	5	–1.76

[a]) pmp and PNa denote *para*-methoxyphenyl and *para*-nitroanilide, respectively.

These observations demonstrate that the rotation barrier along the imidic bond is lowered by the steric bulk and configuration of the 2-position substituents. Furthermore, stereoelectronic effects are also involved in the transition state as inferred by the *Hammett* correlation found for the isomerisation barriers of 2-arylthiazolidines.

These results show that insertion of 2-substituted oxazolidines and thiazolidine in peptides allow the *cis*-content along the imide bond to be tailored. This provides a convenient tool to understand the steric and stereoelectronic effects involved in the *cis-trans* isomerisation of imide bonds. In contrast to the proline residue [9], the *cis*-content seems to be less sequence-dependent, and, consequently, ΨPro can serve as β-turn mimetics.

β-Turn Induction

Since 2,2-dimethylthiazolidine-containing peptides exhibit an extraordinary high *cis*-content (99%), we investigated the induction of the biologically important type VI β-turn motif [10] in cyclopentapeptides. Insertion of 2,2-dimethylthiazolidine results in cyclopeptides with homogeneous conformational state. 2D-NMR Analysis demonstrates that the imide bond adopts the *cis*-geometry in very high content (>98%) and that the peptide backbone is constrained to a β-turn type VIb. In comparison with proline-containing cyclopeptides, this provides an unique opportunity to study and characterise these important β-turn motifs. Study of the impact of β-turn type VI in biologically active peptides is underway and will be reported in due course.

Conclusion

(4*S*)-oxazolidine- and (4*R*)-thiazolidine-4-carboxylic acids (ΨPro) represent new branched proline analogues in which variation of the substituents (R^1, R^2, R^3) results in different physicochemical and conformational properties. The study of the influence of the steric bulk and stereochemistry of the 2-position substituents (R^1, R^2) upon the *cis-trans* ratio along the imide bond demonstrates that ΨPro can efficiently serve as proline surrogate to constrain the backbone or to tailor the *cis*-to-*trans* ratio in peptides. Substitution of proline by ΨPro offers promising new means for studying the importance of imide-isomer geometry and bioactivity in protein chemistry and biology.

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