Proline Isomerization

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Structural Properties and Stereochemically Distinct Folding Preferences of 4,5-*cis* and *trans*-Methano-L-Proline Oligomers: The Shortest Crystalline PPII-Type Helical Proline-Derived Tetramer

*Gilles Berger, Miguel Vilchis-Reyes, and Stephen Hanessian**

Abstract: *The synthesis, structural properties, and folding patterns of a series of* L*-proline methanologues represented by cis- and trans-4,5-methano-*L*-proline amides and their oligomers are reported as revealed by X-ray crystallography, circular dichroism measurements, and DFT calculations. We disclose the first example of a crystalline tetrameric proline congener to exhibit a polyproline II helical conformation. Experimental evidence of PPII-type helical arrangement (both in solution and in the solid state) of cis-4,5-methano-*L*-proline oligomers is supported by theoretical calculations reflecting the extent of n→π* stabilization of the trans-amide conformation.*

Proline residues are of high importance in the conformational heterogeneity of proteins, notably by the presence of both *cis* and *trans* conformations of their peptide bonds. Indeed, the cyclic nature of proline imposes structural constraints, which comprise a higher frequency of *cis* peptide bonds (approx. 5%) compared to other amino acids (less than 0.1%).[1–4] Moreover, *cis–trans* isomerization of proline amide bonds are involved in many biological processes, such as ligand recognition, protein folding, and ligand-gated ion channel opening.[5–10]

Apart from the *cis–trans* conformations of the Xaa-Pro peptide bonds, the pyrrolidine ring of proline residues can adopt either a C_γ-*endo* or C_γ-*exo* pucker conformation. Indeed, C_γ experiences large out-of-plane displacement, and this ring-puckering seems to be correlated to the *trans*/*cis* amide ratio ($K_{T/C}$).[3,11–13] Highly populated C_γ-exo puckers exhibit high $K_{T/C}$, whereas high populations of C_γ-endo puckers are associated with lower $K_{T/C}$ values.[14] Among other parameters, these observations are rationalized by greater n→π* hyperconjugative delocalization in *exo*-puckered proline. Relevant dihedral angles and conformations that define the structural properties of proline are depicted in Figure 1.

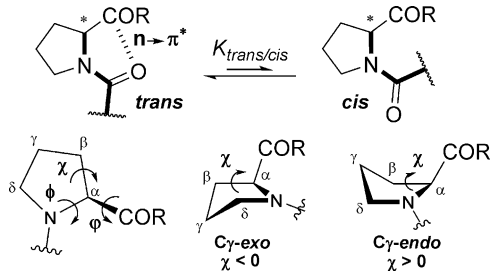

Figure 1. a) *Cis–trans* isomerism of the Xaa-Pro amide bond. b) Important dihedrals for proline conformations.

Both in the solid state and in solution, poly(Pro) peptides adopt helical conformations, known as polyproline I (PPI) and polyproline II (PPII). PPI is a compact, right-handed helix with all its residues adopting a *cis*-amide conformation with characteristic φ and ψ angles around −75° and +160°, and associated with a helical pitch of 5.6 Å. PPII exists in a looser, left-handed helix of *trans*-amide bonded residues with dihedral angles φ and ψ around −75° and +145°; the pitch of the helix is around 9.4 Å, making it less compact than the PPI helix.[15–18]

PPII is known to occur in unordered peptides, globular proteins, the structural protein collagen, and short oligopeptides.[18–25] Despite its name, the PPII-type helical arrangement can also be found in poly(Glu), poly(Lys), poly(Ala) peptides, and in many other regions of proteins.[26] Local PPII-type secondary structures have been shown to be of crucial importance in protein structure and function.[19] PPII-type helicity is favored in aqueous media,[21,27,28] whereas a PPI conformation is more stable in the absence of coordinating water molecules.[29]

Previous studies from our laboratories have shown that the pyrrolidine ring in *cis*- and *trans*-4,5-methanoprolines is essentially planar compared to proline itself, as evidenced by single crystal X-ray crystallography.[30] We surmised that the conformational constraint imparted by the fused cyclopropane ring could affect the properties of prolylamides in several ways. For example, changing the dihedral angles could profoundly affect the hybridization level of the nitrogen atom (planar or pyramidal), with consequences reflected in the *cis–trans* isomerism of the amide bond. We were also intrigued by the prospects of replacing proline residues in known drugs by *cis*- and *trans*-4,5-methanoprolines to probe the spatial requirements of the pyrrolidine ring within the active site of a relevant enzyme. Indeed, the *cis*- and *trans*-4,5-methano-L-proline counterparts of the antihypertensive drug captopril, an inhibitor of the angiotensin converting enzyme (ACE),[31]

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were equally active nM inhibitors.[32] In another context, conformationally constrained indolizinones containing a fused cyclopropane enhanced the antibacterial activity of ceftazidime, most likely acting as an inhibitor of a β-lactamase.[33] More recently, the marketed antidiabetic drug Onglyza (saxagliptin), a dipeptidyl peptidase-4 (DPP4) inhibitor, contains a 4,5-methano-L-prolylnitrile as an important core subunit.[34,35] Incorporation of the 4,5-fused cyclopropane ring in saxagliptin was critical in prolonging the half-life of the drug compared to the L-prolylnitrile prototype.

Herein, we report the synthesis and structural properties of *cis*- and *trans*-4,5-methano-L-proline amides and oligomers (Figure 2) as revealed by X-ray diffraction (XRD), circular

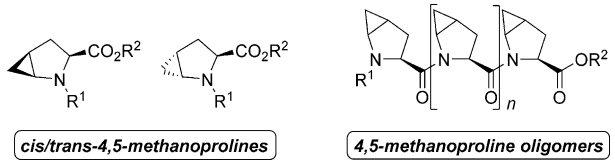

Figure 2. *Cis*- and *trans*-4,5-methano-L-prolines and their oligomers used in the present study.

dichroism (CD), and density functional theory (DFT) calculations. We also disclose the shortest example of a crystalline tetrameric proline congener to exhibit a polyproline II helical conformation. We hasten to add that whereas tetrameric prolines have been reported, their capacity to adopt a PPII helical conformation is not conclusive.[36,37]

The *cis*- and *trans*-4,5-methano-L-prolines were obtained according to previously published procedures (see Supporting Information for more details).[32,38,39] Monomeric 4,5-methanoprolines were then coupled to obtain their *N*-Boc di-, tetra-, and hexamers as ethyl esters, to study their conformations both in the solid state and in solution, using X-ray crystallography and CD, respectively.

Obtaining crystalline forms of relatively short oligoprolines and the study of their 3-D conformational properties in the solid state has been the Achilles heel in the quest to obtain PPII helical motifs. After considerable effort, Wennemers and co-workers[40] succeeded in obtaining the crystal structure of the first oligoproline PPII helix comprising only six residues as the *p*-bromobenzoyl amide.

We started our investigations with the study of dimeric *cis*- and *trans*-4,5-methano-L-prolines (Figure 3).

Examination of the crystal structure of the *cis*/*cis* dimer **1a** shows structural parameters in agreement with the initiation of a PPII helix (Figure 3a). The amide adopts a *trans* conformation with a ψ angle around 165°. The distances between the donor amide oxygen atom and the acceptor ester carbonyl (d) are substantially less than the sum of their Van der Waals radii (3.22 Å), supporting the existence of a typical n→π* interaction, known to stabilize this conformation.[13,23,29,42–49] Indeed, d_1 and d_2 are 2.92 and 3.04 Å, respectively, highlighting strong n→π* delocalization. When examining the crystal structures either of the *trans*/*trans*-methano-L-proline dimer **1b** or the mixed *trans*/*cis*-methano-L-proline dimer **1c**, d_1 and d_2 are still less than the sum of Van der Waals radii but not as much as in **1a**. This observation

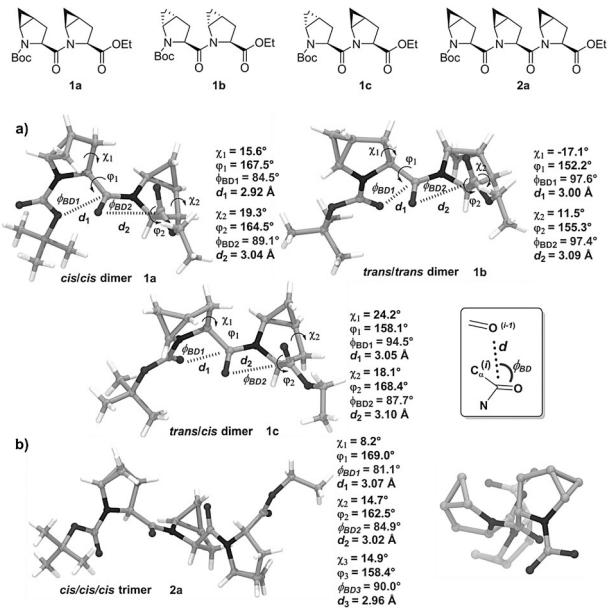

Figure 3. a) Single-crystal structures of *cis*/*cis*, *trans*/*trans*, and *trans*/*cis* N-Boc-MPro-MPro-CO_2Et dimers. b) X-ray of trimeric N-Boc-*cis*-4,5-methano-L-proline ethyl ester.[41]

strongly suggests that the n→π* stabilization of the *trans*-amide conformation is weakened when *trans*-4,5-methano-L-prolines are involved. The angles between the amide oxygen and the acceptor ester carbonyl (bearing the antibonding orbital) in these structures are found between 84.5° and 97.6°, and differ from the ideal Bürgi–Dunitz trajectory for an n→π* interaction, which is around 104°.[40,50] Further insight into these interactions was provided from the DFT structures of the dimers and natural bond orbital (NBO) analysis (see below).

We also obtained crystals from the trimeric *cis*-4,5-methano-L-proline **2a** which further exhibit the progression of the amide folding pattern to form PPII-like peptide bonds (Figure 3b).

Encouraged by this result, we were able to crystallize the tetrameric *cis*-4,5-methano-L-proline as the methyl ester hydrochloride salt **3a**, and to obtain a crystal structure showing the expected features of a PPII-type helix (Figure 4b).

A quasi-C_3 symmetry along the helical axis is observed with a helical pitch of 9.1 Å, so that each methanoproline residue accounts for about 3 Å. When compared to the recently published X-ray structure of the oligoproline hexamer by Wennermers and co-workers,[40] the tetrameric *cis*-4,5-methano-L-proline helix is very similar (Figure 4c). The crystals belong to the monoclinic $C121$ space group ($\beta = 95.89°$, $V = 2848.0$ Å^3), and the structure was solved by direct methods to atomic resolution. No inclusion of solvent was observed, however the assembly is stabilized by a central double column of chloride ions, facing the ammonium moieties of two tetramers in a head-to-head fashion.

The folding pattern of the synthesized oligomers into PPII-type helices in solution was studied by means of circular dichroism. The characteristic CD signature of a PPII-type

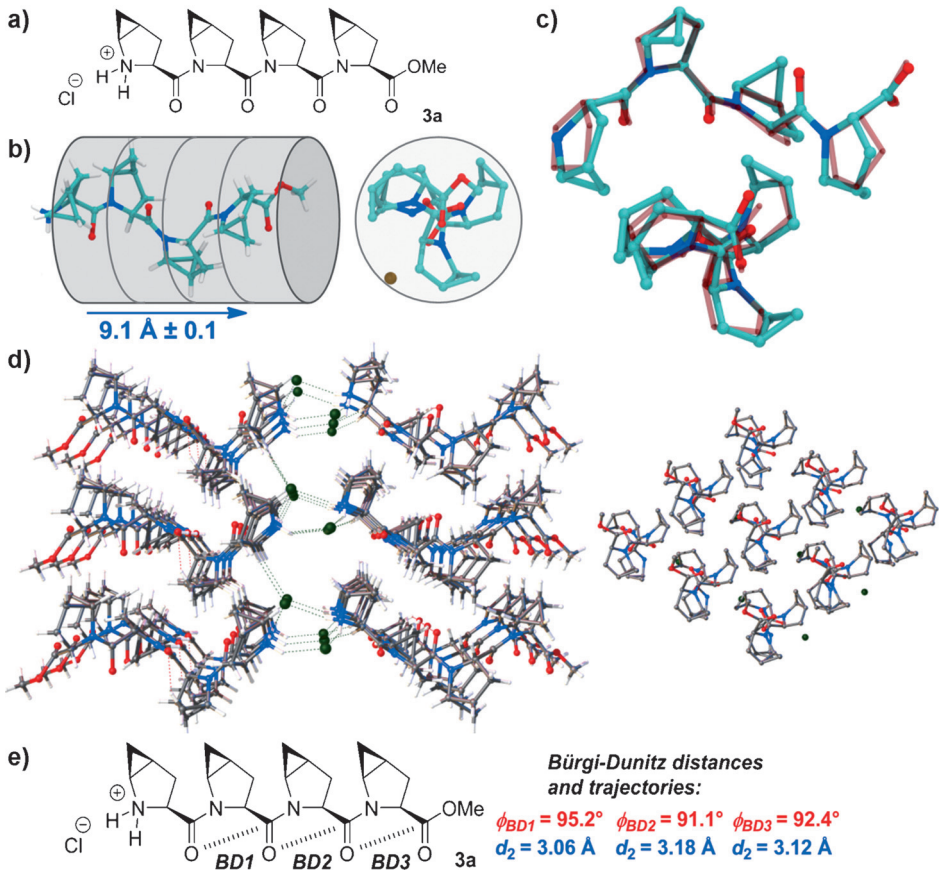

Figure 4. a) Tetrameric *cis*-4,5-methano-L-proline methyl ester hydrochloride **3a**. b) Side-view and view along the helical axis of the crystal structure showing a typical polyproline II helix conformation. c) Fitting of our tetrameric crystal structure to the hexameric oligoproline from Wennemers and co-workers.[40] (fitting to heavy atoms only, RMSD = 0.34 Å). d) Packing shows central chloride ions interacting with surrounding N–H and C_α–H bonds. e) Bürgi–Dunitz distances and trajectories.[41]

helix, which consists in a strong negative band at 206 nm and a positive band around 225 nm[15,51–53] can be recognized for both the all-*cis*-tetramer **4a** and the corresponding hexamer **5a** in Figure 5. Clearly, as the numbers of residues increase, the *cis*-4,5-methano-L-proline oligopeptides assemble into the typical PPII-type helix, with as few as four residues. Very importantly, the *trans* derivatives remain disordered under these conditions (Figure 5).

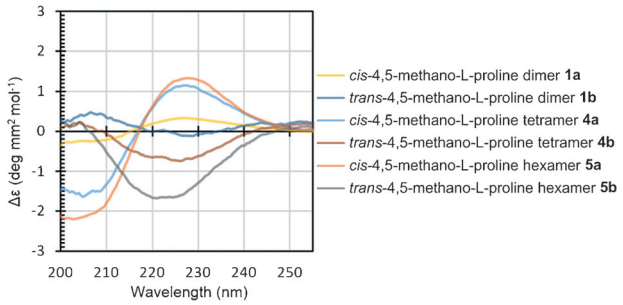

Figure 5. CD spectra of *cis*- and *trans*-4,5-methano-L-proline oligomers in MeOH/$CHCl_3$ 99.9:0.1, showing the typical polyproline II spectrum for the *cis* derivatives, whereas the *trans* isomers remain disordered under the same conditions. Structures of the tetramers **4a**,**b** and the hexamers **5a**,**b** are not shown (see the Supporting Information).

Subsequent geometry optimization of the dimers **1a–c** at the DFT level (ωB97x-D/def2-TZVP;[54–56] for details see the Supporting Information) followed by NBO analysis[57] provided the energetic contribution from the n→π* stabilization of the *trans*-amide bonds (Figure 6).

Hyperconjugative delocalizations arising in the *cis*-4,5-methano-L-proline dimer **1a** are both found at about 1.5 kcal mol^{-1}, thereby providing an overall stabilization of the *trans*-amide conformation. However, stabilization arising from these delocalizations is substantially decreased for the *trans*-4,5-methano-L-proline dimer **1b**, as one of the two n→π* energetic contributions drops to zero. The same observation is made for the mixed *trans*-4,5-methano/*cis*-4,5-methano compound **1c**, so that dimers containing *trans*-4,5-methano-L-proline moieties experience decreased stabilization of their *trans*-amide conformation. This could explain the propensity of the *cis*-4,5-methano-L-proline oligomers with *trans*-amide orientations to arrange in solution as PPII-type helices, in contrast to the *trans*-4,5-methano-L-proline oligomers (see CD in Figure 5).

To verify this hypothesis for larger and more relevant structures, tetramers **3a** (the crystalline *cis*-4,5-methano-L-proline tetramer) and **3b** (its all-*trans*-4,5-methano counterpart) were DFT-optimized. NBO analysis interestingly shows that in the case of the **3a**, each residue participates in a strong n→π* interaction (around 1 kcal mol^{-1} each and a total contribution of 3 kcal mol^{-1}), whereas very limited energetic effect is gained from these delocalizations in **3b** (total contribution around 0.5 kcal mol^{-1}). This leads to a critical destabilization of the PPII conformation in **3b** with respect to the *cis*-4,5-methano congener **3a**.

As a comparison, the calculations were also run for the L-proline tetramer. The sum of the calculated n→π* stabilization energies for this L-proline tetramer (not shown) were found to be about 1 kcal mol^{-1}, thus lying in between the structures generated from *cis*-4,5-methano-L-prolines **3a** ($\Sigma\Delta E_{n\to\pi^*} = 3.0$ kcal mol^{-1}) and *trans*-4,5-methano-L-prolines **3b** ($\Sigma\Delta E_{n\to\pi^*} = 0.5$ kcal mol^{-1}).

As previously stated, another dramatic conformational effect arising upon the introduction of a cyclopropane in the 4,5-position of L-proline is the considerable flattening of the

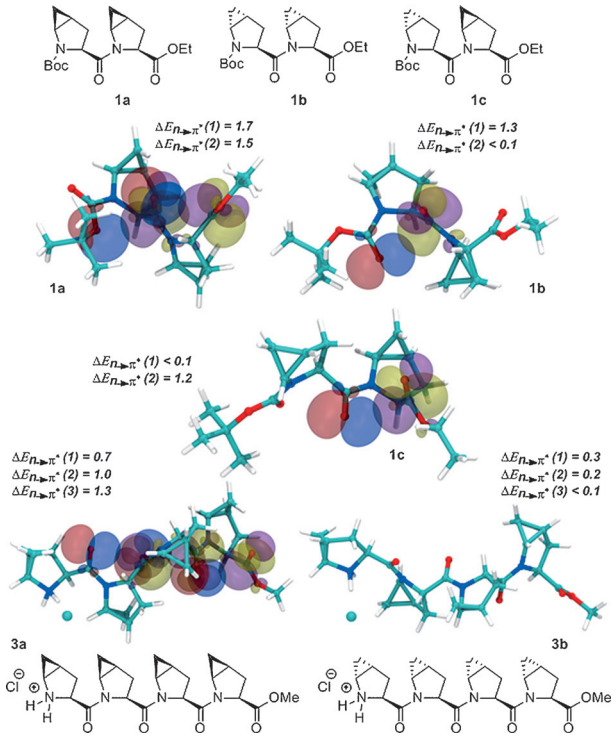

Figure 6. NBO analysis of the n→π* interactions arising in the dimeric structures of *cis*-4,5-methano-L-proline **1a** (left), *trans*-4,5-methano-L-proline **1b** (right), mixed *trans*/*cis* dimer **1c** (middle), and the tetrameric structures **3a** and **3b** (bottom left and right). Labeling of stabilization energies $\Delta E_{n\rightarrow\pi^*}$ (kcal mol^{-1}) are from N- to C-terminal residues. Lone pairs (n electrons) and π antibonding (π* electrons) NBO are respectively displayed as blue/red and purple/yellow (isovalue = 0.03 au). NBO are not displayed for interactions energies falling below 0.5 kcal mol^{-1}. All of the calculations were run at the ωB97x-D/def2-TZVP level of theory.

pyrrolidine ring, where it becomes almost planar.[30] Flattening of the pyrrolidine ring in 4,5-methano-L-prolines was therefore investigated in the light of NBO analysis through the atomic hybrids forming the bonding orbitals, using *N*-acetyl-L-proline ethyl ester, *N*-acetyl *cis*- and *trans*-4,5-methano-L-proline ethyl esters as model compounds (Supporting Information). Analysis of the results reveal that the carbon atoms of the cyclopropane ring directly fused to the pyrrolidine moiety in *cis*- and *trans*-*N*-acetyl 4,5-methano L-proline ethyl esters appear to have a stronger sp^2-type C–H bonding, being almost in the plane of the pyrrolidine ring. Indeed, NBO hybrids of these C–H bonds show a balanced sp^3/sp^2 character (around sp$^{2.5}$) in agreement with the flattening of the ring, whereas the same bonding orbitals in the L-proline equivalent structure involve hybrids with strong sp^3 character. N–C bonds are also found to be shorter for the *cis*- and *trans*-4,5-methanoproline congeners, as observed from the X-ray data (Supporting Information), highlighting the increased sp^2 character of the N–C$_\delta$ bonds in the cyclopropanated structures. On the other hand, angular constraints from the three-membered ring impose a strong p character to the C$_\gamma$–C$_\delta$ bonding hybrids (around 80% p character on both carbons). Considering the NBO delocalization, the *trans*-4,5-methano *N*-acetyl congener lacks an efficient n→π* interaction. Also, a strong correlation is found for the distance between the donor amide oxygen and the acceptor carbonyl carbon, as in the *cis*- 4,5-methano *N*-acetyl congener, where the distance is significantly shorter when the interaction is stronger, an observation already made when comparing crystal structures of the dimers **1a–c** (that is, their Bürgi–Dunitz distances with calculated n→π* energetic contributions).

In conclusion, we have demonstrated for the first time that as few as four *cis*-4,5-methano-L-proline residues in a tetrameric oligopeptide can adopt a PPII helical arrangement in the solid crystalline state. Geometrical factors affecting the n→π* interactions between the amide carbonyl and the ester carbonyl from adjoining residues are crucial parameters for adopting PPII-type helicity, which is also corroborated by DFT calculations. This is in agreement with the CD data showing that *cis*-4,5-methano-L-proline oligomers form PPII-type helices, whereas the *trans* counterparts remain disordered. A number of important applications can be envisaged based on these results, such as tuning the stability of PPII regions of peptides by substituting proline residues by their *cis*- or *trans*-4,5-methano congeners. Replacing proline residues with their 4,5-methanologues can be a useful structural variation to optimize spatial, stereoelectronic, and conformational effects in the design of modified drugs and peptides. In the latter case, one can imagine stabilizing PPII helicity in peptide or proteins with *cis*-4,5-methano-L-proline segments, while destabilizing such secondary structures using *trans*-4,5-methano-L-proline counterparts. Studies related to these and related variations in the nature of the residues are in progress.

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