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Ring Pucker Control in β-Prolines

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Introduction

Pyrrolidine ring puckering influences proline localization in peptide conformations.[1, 2] The dihedral angles χ^1 and χ^2 define respectively the C^γ *endo* ($\chi^1 > 0$, $\chi^2 < 0$) and *exo* ($\chi^1 < 0$, $\chi^2 > 0$) puckers.3-6 In peptides, proline (e.g., **1**) prefers usually the C^γ *endo* ring pucker with the C^α carbonyl in the pseudoaxial orientation (**Figure 1**). Pyrrolidine ring substituents can significantly influence proline puckering and consequently peptide folding.[3-6] For example, (4*R*)-*trans*-hydroxy- and fluoro-prolines favour the *exo* over the *endo* ring pucker in peptides due to stereoelectronic effects.[5] Moreover, *N*-acyl (4*R*)-*trans*- and (4*S*)-*cis*-*tert*-butyl prolines adopt respectively *endo* and *exo* ring puckers.[6]

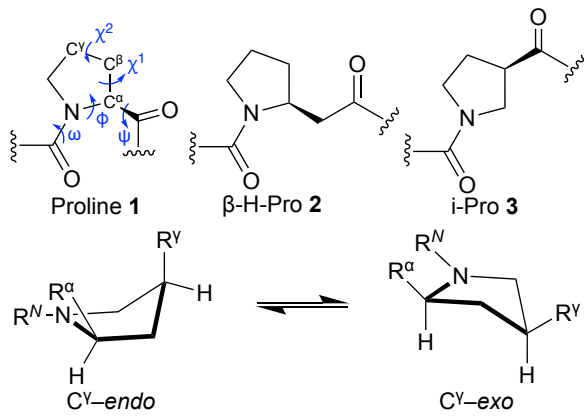

Figure 1. Prolyl and β-prolyl residues and related pyrrolidine ring puckerings.

The *N*-acetyl analogs of the β-prolines, β-homoproline and isoproline (e.g., **2** and **3**) are predicted to adopt preferred *exo* puckering with pseudoequatorial orientations of the respective C^α and C^β substituents.[7, 8] Exploring the synthesis and conformational preferences of homo-isoproline (Hip) chimeras, we have characterized influences of nitrogen hybridization on ring puckering and peptide topology.

Results and Discussion

The effects of nitrogen hybridization on ring puckering and conformation were examined using di-*N'*-methyl amides of *N*-toluensulfonyl (Ts) and *N*-*p*-nitrophenyl (*p*Np) *cis*-homo-isoprolines *cis*-Ts-Hip(NHMe)-NHMe (**4**) and *cis*-*p*Np-Hip(NHMe)-NHMe (**5**), which were respectively synthesized and characterized by ^{1}H NMR spectroscopy and X-ray crystallography.[9] In sulfonamide **4** the nitrogen is sp^3 hybridized and the *exo* ring pucker is favoured due in part to pseudoequatorial orintations of the C^α and C^γ substituents which minimize steric repulsion (**Figure 2**). Sulfonamide **4** exhibited spectral and crystallographic data for χ^1 and χ^2 dihedral angles in agreement with an *exo* ring pucker as previously reported for 4-substituted prolines.[6] *p*-Nitrophenyl analog **5** is expected to adopt the sp^2 nitrogen hybridization and induce $A^{1,3}$ strain with the C^α substituent which takes a pseudo-axial orientation eclipsing the C^β proton in a flattened C^γ *exo* ring pucker as characterized by X-Ray crystallography (**Figure 2**). The application of the ring puckering effects of homo-isoproline are under further study in peptide mimics.[9]

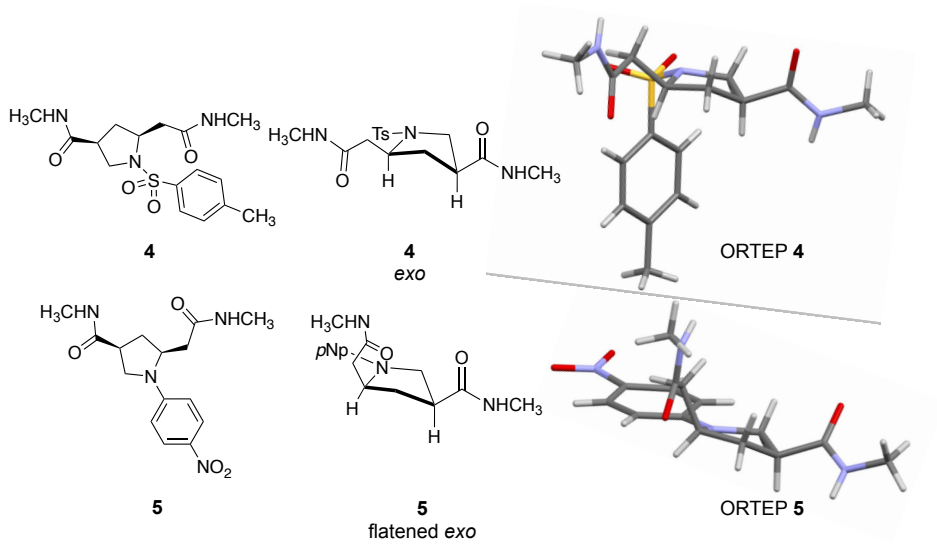

Figure 2. *N*-Substituted homo-isoproline diamides **4** and **5** and favored ring puckerings.

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