TURNING PEPTIDE STRUCTURES USING NITROGEN CHIRALITY

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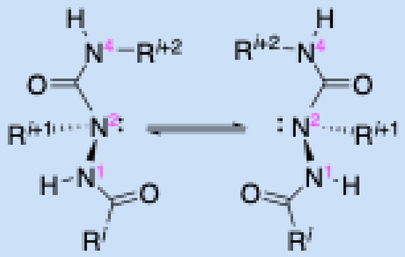
ABSTRACT

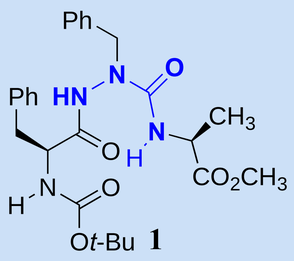
Pyramidal N^2-nitrogen in semicarbazide residues facilitates folding in turn conformers. Factors governing N^2-pyramidalization are being explored in azapeptides using NMR spectroscopic and X-ray crystallographic methods.

INTRODUCTION



Pyramidal nitrogen has been studied in aziridine and cyclic amine derivatives with focus on parameters such as steric effects, hyperconjugation, ring constraints, and *N*-substitution.[1, 2] In semicarbazide analogs, such factors have yet to be itemized, to the best of our knowledge.

Preliminary observations of semicarbazide X-ray structures indicate that N^1 and N^4-nitrogen are typically sp_2 hybridized and flat, but the N^2-nitrogen can be relatively pyramidal and favor folding into turn conformers in azapeptides.



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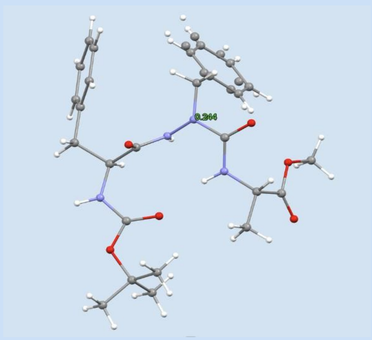
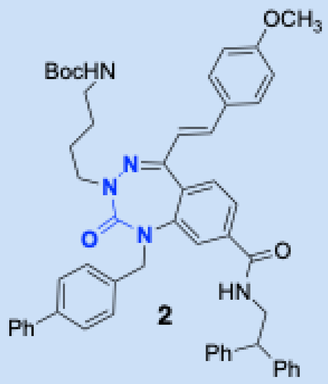


- Substitution at N^2 may decrease pyramidalization: e.g., Ac-Ala-azaGly-NHMe (d = 0.283 Å, computational data)[3] vs Boc-Phe-azaPhe-Ala-OMe (**1**, d = 0.244 Å); the aza-residue exhibited *R* configuration and βII-turn torsion angle values.[4]

Ring size influences N^2 pyramidalization in cyclic aza-residues: e.g., Boc-Ala-aza-Proline-NH-*i*Pr (d = 0.389 Å),[5] and Boc-Ala-aza-Pipecolate-NH-*i*Pr (d= 0.309 Å)[9] exhibited *S*-configuration with βIV-turn torsion angle values.[5, 9]



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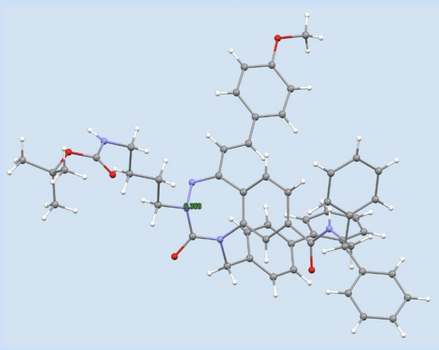
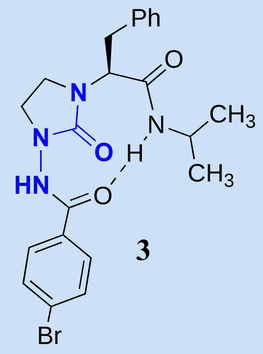


Moreover, 7-membered 1,3,5,8-tetrasubstitued benzotriazepin-2-one (**2**, d = 0.358 Å) without stereogenic carbon exhibited propensity to mimic βI and I′-turns due in part to dynamic N^2 chirality.[6]



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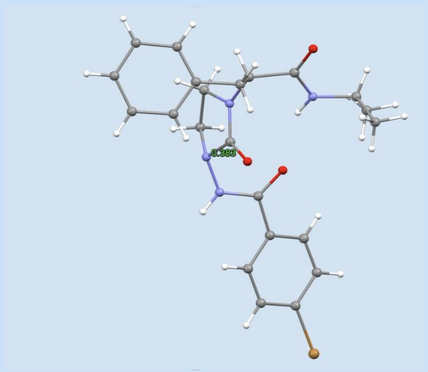
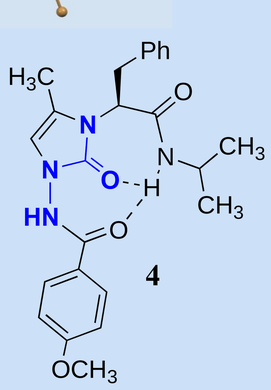


Ring strain can decrease N^2 pyramidalization in aza-lactam dipeptide analogs: e.g., *N*-amino-imidazolidinone (Aid) peptide **3** (*p*-BrBz-Aid-Phe-NH*i*-Pr, (d = 0.383 Å) adopted βII and II′-turns with dynamic N^2 chirality.[7]

The presence of allylic strain reduced N^2 pyramidalization in *N*-amino-imidazol-2-one (Nai) peptide **4** (*p*-MeOBz-(4-Me)Nai-Phe-NH*i*-Pr) which adopted βII'-(d = 0.243 Å) and γ-turn (d = 0.116 Å) conformers.[8]



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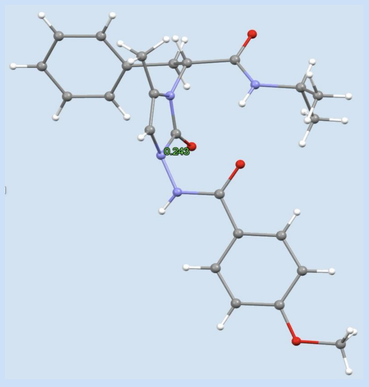
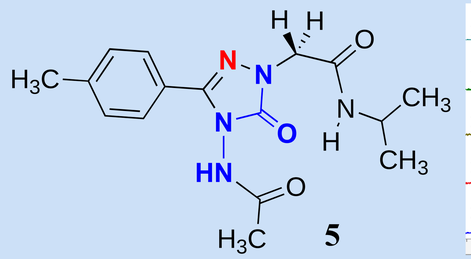


DISCUSSION

Mindful of such parameters, we are studying influences of N^2 pyramidalization on the nitrogen interconversion barrier and peptide conformation in semicarbazide analogs.

The consequence of replacing the Nai C4 carbon with nitrogen is under study using 4-aza-Nai analogs: Ac-4-aza-(*p*-MePh)Nai-Gly-NH*i*-Pr (**5**) and Ac-4-aza-(*p*-MePh)Nai-Gly-O*t*-Bu (**6**), exhibited diastereotopic methylene proton signals.



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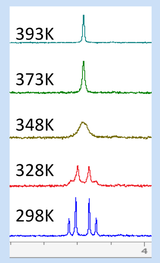
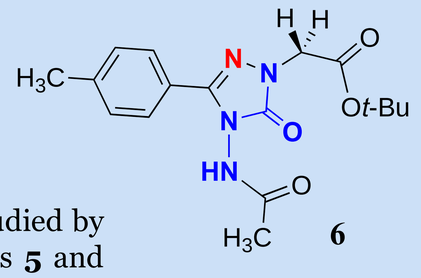


($\Delta G^{\neq}$) = 18 kcal/mol

Changes in amide chemical shift value as a function of DMSO-d_6 (0.1 to 100%) in $CDCl_3$ indicated that the isopropyl amide proton in 4-aza-Nai peptide **5** is solvent shielded compared to the hydrazide proton indicating a turn conformer.



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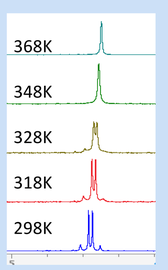

($\Delta G^{\neq}$) = 22 kcal/mol

The nitrogen inversion barrier ($\Delta G^{\neq}$) was studied by VT-NMR experiments on 4-aza-Nai peptides **5** and **6** and coalescence of diastereotopic methylene proton signals was observed.

CONCLUSION & PERSPECTIVES

- 4-Aza-Nai peptides **5** and **6** were synthesized and are being studied to examine the factors influencing N^2-nitrogen pyramidalization and peptide folding.
- Amide proton chemical shift with solvent polarity and diastereotopic methylene proton signal correlation indicate 4-aza-Nai peptides **5** adopts a turn conformer with a lower barrier to nitrogen inversion than relatively more electron deficient ester **6**.
- In the future, aryl substituent impact will be investigated on 4-aza-Nai residue N^2-pyramidalization.
- Crystals and X-ray analyses of 4-Aza-Nai peptides **5** and **6** are being pursued to confirm conformational effects of N^2-pyramidalization.

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ACKNOWLEDGEMENTS

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