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The Semicarbazone Peptidomimetic Group in Imino Aza Peptides

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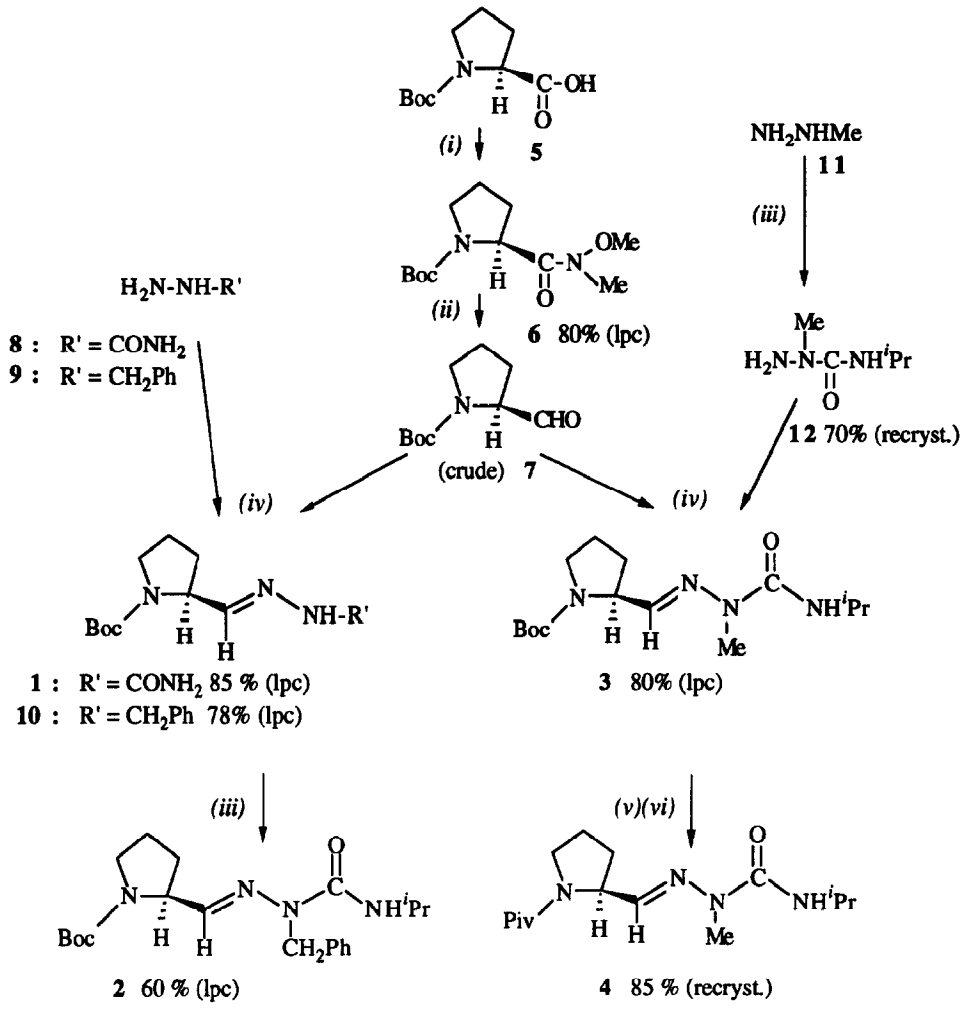
Abstract: *The semicarbazone moiety (C-CH=N-NR-CO-NH-C), either obtained by coupling a peptide aldehyde with a semicarbazide, or by action of an alkylisocyanate on a peptide hydrazone, is a dipeptide isostere. The structure of four imino aza dipeptides, analogues of the Pro-Gly, Pro-Ala and Pro-Phe dipeptides, has been studied in solution by ^{1}H-NMR and IR spectroscopy, and in the solid state by X-ray diffraction.*

Various peptide isosteres have been proposed for the design of bioactive peptide analogues, aiming at less biodegradable and geometrically constrained molecules. The Z-ethylene (-CH=CH-) junction has been claimed to be an excellent trans-amide isostere, but the difficulty in obtaining the adequate chirality for the contiguous α-carbons is probably responsible for the small number of examples reported so far.[1-3] The trans imino link (-CH=N-) is more easily obtained,[4] but its weak stability is well-known. We propose the more stable semicarbazone moiety (C^{α}-CH=N-N^{α}(R)-CO-NH-C^{α}) as a dipeptide surrogate. It is easily obtained either by coupling a peptide aldehyde with a semicarbazide, or a peptide hydrazone with an isocyanate.

In order to investigate the chemical and structural aspects of this new class of pseudopeptides that we propose to call imino aza peptides, we have prepared the compounds **1-4** (Scheme 1). Their general formula RCO-Proψ[CH=N]AzXaa-NHR' (R, R', Xaa = ^{t}BuO, H, Gly (**1**); ^{t}BuO, ^{i}Pr, Phe (**2**); ^{t}BuO, ^{i}Pr, Ala (**3**); ^{t}Bu, ^{i}Pr, Ala (**4**)) according Spatola's nomenclature,[5,6] where ψ[CH=N] means that the imino group has been substituted for the amide bond between proline and AzXaa, the aza analogue of the Xaa α-amino acid,[7] has the advantage of making apparent the analogy with the cognate peptide sequence. All four imino aza peptides have been submitted to IR and ^{1}H-NMR experiments in solution. Compounds **1** and **4**, having grown single crystals, have been studied by X-ray diffraction.

The synthesis of derivatives **1-4** is summarized in Scheme 1. Boc-prolinal **7** is classically prepared by reduction of the N,O-dimethylhydroxamide by $LiAlH_4$.[4] **1** is obtained by action of semicarbazide on **7** at room temperature. In the same conditions, the coupling of **7** with the semicarbazide **12** (directly obtained from methylhydrazine **11** and isopropylisocyanate) gives the Pro-Ala imino aza analogue **3**. TFA acidolysis of the

Boc group in **3**, followed by action of the pivaloyl chloride, leads to **4**. The same procedure with benzylhydrazine failed for the synthesis of the Pro-Phe imino analogue **2**. We first condensed **7** with benzylhydrazine to obtain the peptide hydrazone **10**, which was later coupled to isopropyl isocyanate. All derivatives in Scheme 1, except Boc-prolinal **7** which has been used without further purification, are chromatographically pure and give satisfactory ^{1}H-NMR data. Derivatives **1** and **4** have grown single crystals by slow cooling of an ethanol solution.



Scheme 1.[6] *(i)* 1: ^{i}BuOCOCl / NMM / CH_2Cl_2 / -15°C / 1h, 2: HCl,NHMe-OMe / NMM; *(ii)* $LiAlH_4$ / THF / -15°C; *(iii)* ^{i}PrN=C=O / THF / 63°C / overnight; *(iv)* EtOH / AcONa / r.t. / overnight; *(v)* TFA / r.t. / 15 mn; *(vi)* PivCl / NEt^iPr_2 / CH_2Cl_2 / 0°C.

Resolution of the crystal structures of **1** (with three non-equivalent molecules **1A**, **1B** and **1C** in the asymmetric unit) and **4** by X-ray diffraction shows that the dimensions of the imino aza group are rather similar to the standard peptide values (Fig. 1), with a $C^{\alpha}\cdots N^{\alpha}$ distance of 3.58 Å in the former, compared to the

C^{α}···C^{α} distance of 3.81 Å in the latter.[8] All four molecules **1A**, **1B**, **1C** and **4** exhibit very similar, nearly planar conformations of the semicarbazone fragment, with the C=O bond trans to the N-N bond (Fig. 2). In this planar conformation, the C-terminal trans amide N-H hydrogen is directed towards the (sp^2) nitrogen lone-pair. The **1A** and **1B** molecules are almost identical, but differ from the **1C** and **4** molecules by the orientation of the proline cycle relative to the semicarbazone plane (Fig. 2), with a pseudo ψ (N-C^{α}-C=N) dihedral angle of 134° (**1A**), 135° (**1B**), -100° (**1C**) and -20° (**4**). The three molecules of **1** also differ from **4** by the cis Boc-Pro amide bond in the former compared to the trans Piv-Pro amide bond in the latter.

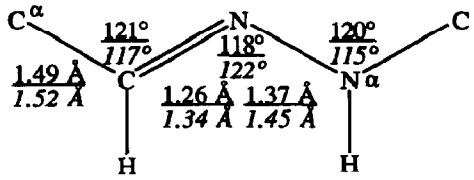


Fig. 1. Compared average bond lengths and bond angles for the imino aza (roman) and peptide[8] (italics) groups

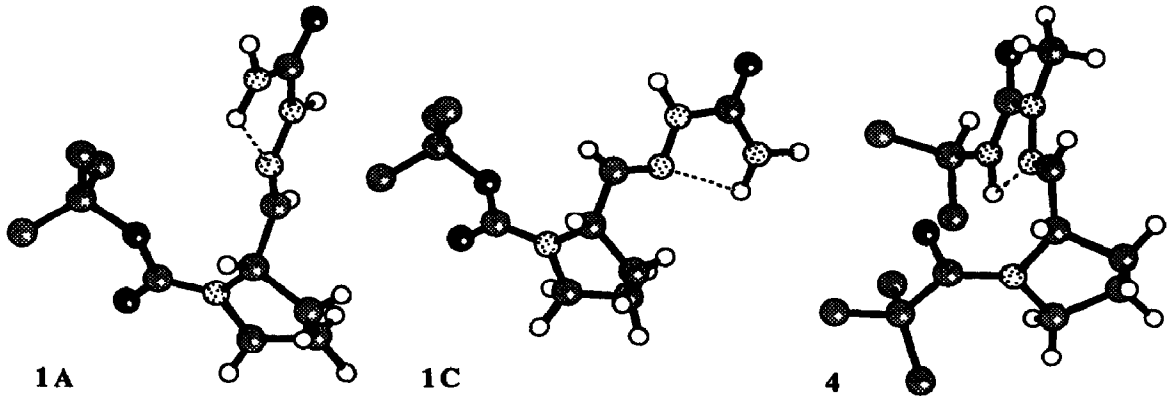


Fig. 2. Crystal molecular conformations of **1A**, **1C** and **4** showing the three relative dispositions of the pyrrolidine and cis planar semicarbazone fragments.

In $CDCl_3$ solution, ^{1}H-NMR reveals a cis-trans equilibrium for the Boc-Pro amide bond in derivatives **1-3**, and a trans Piv-Pro amide bond in **4**. In four cases, the very small sensitivity to the solvent composition ($CDCl_3$ / DMSO-d_6 mixtures) of the C-terminal N-H proton trans to the semicarbazone carbonyl bond (6.29 ppm in $CDCl_3$ and 6.32 ppm in DMSO-d_6 for **4**) indicates its involvement in a very stable intramolecular hydrogen bond. The (Piv)C=O stretching frequency (1619 cm^{-1} in CH_2Cl_2 and 1616 cm^{-1} in DMSO) is typical of a free vibrator.[9] Surprisingly, the C-terminal N-H stretching frequency is neither affected by the solvent (3417 cm^{-1} in CH_2Cl_2 and 3412 cm^{-1} in DMSO), and is only a little shifted (less than 20 cm^{-1}) to lower frequencies with reference to the free (iPr)N-H vibrator in related peptides.[9] We therefore conclude the retention in solution of the intramolecular N-H···N interaction closing a 5-membered cycle, already present in the crystal, and hence the cis planar conformation of the semicarbazone fragment. The (Pro)C^{α}H-CH vicinal coupling

constant of 4.0 Hz for **4** in $CDCl_3$ is rather small and could correspond to a proton-proton dihedral angle of about 60° or 120°,[10] but is hardly assignable to a definite pseudo ψ angle value.

The semicarbazone fragment can be considered as a dipeptide isostere with a cis planar conformation stabilized by an intramolecular N-H···N interaction involving the lone-pair of the imino nitrogen as the accepting site.[11] The stability of this planar structure is remarkable, as other similar small peptide analogues are generally flexible in a so strong aprotic medium as DMSO.[12] The various relative orientations of the semicarbazone plane and proline cycle also deserve to be noted, and three different molecular conformations have been observed in the solid state (Fig. 2). Despite the absence of a hydrogen bond of the i+3 → i type, **4** assumes a folded structure in the solid state with a short distance of 4.97 Å between the extreme α-carbons, similar to that encountered in the peptide β-folded structure.[13]

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6. The following abbreviations are used: AzXaa, aza analogue of Xaa α-amino acid (N substituted for C^{α}); Boc, *tert*-butyloxycarbonyl; DMSO, dimethylsulfoxide; DMSO-d_6, hexadeuterated dimethylsulfoxide; lpc, liquid-phase chromatography; NMM, N-methylmorpholine; Ph, phenyl; Piv, pivalyl ; TFA, trifluoroacetic acid; THF, tetrahydrofuran.
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