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Catalytic hydrogenation of vinylogous peptides: a route towards γ-peptide foldamers

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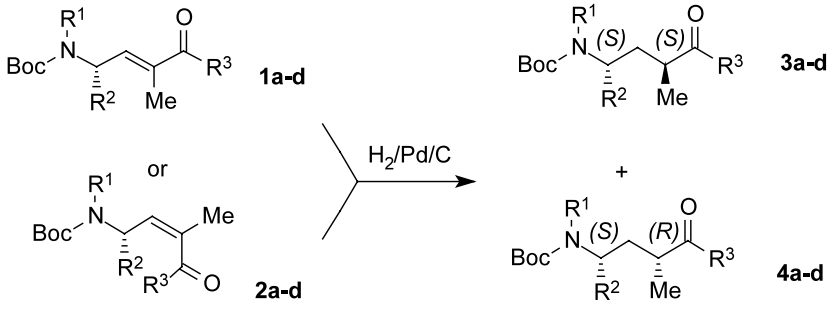
Abstract—Catalytic hydrogenation over Pd/C of vinylogous aminoacids and aminoamides has been studied. The configuration of the ethylenic bond has an important effect on the diastereoselectivity. The higher selectivity is observed with the *E*-vinylogous aminoamides. The conformational preferences of the α,γ-disubstituted γ-peptides have been determined. The 2*S*,4*S*-γ-peptide moiety induces a β-like folded structure stabilized by an intramolecular hydrogen bond, whereas the 2*S*,4*R*-diastereomer assumes an open structure.

A great number of rigid molecules reproducing structural peptide units, and aiming at the design of bioactive peptide analogues with restricted flexibility, have been reported in the literature.[1] Most of them contain covalent rings mimicking folded regions, and more specifically the β-turn, a local structure spanning a tetrapeptide sequence where the carbonyl of the residue in position i is hydrogen-bonded to the NH in position i+3, thus resulting in an *N*-H···O=C H-bond which closes a 10-membered cycle.[2] Actually, these cyclic β-turn mimics often present different chiral centers, and their non-peptidic nature is an obstacle in the modulation of the chirality and the nature of the side chains.[1c,3]

We have already described the synthetic pathways to the vinylogous peptide analogues where either a *Z* or *E*-ethylenic bond is inserted between the α-carbon and the carbonyl of a peptide residue,[4] and reported the 3D-structure of both moieties in the solid state and in solution.[4a] The *E*-ethylene bond in **1d** induces an extended conformation, and the *Z*-ethylene bond in **2d** a folded structure with an N–H···O=C H-bond closing a nine-membered cycle. The catalytic hydrogenation of both *Z* and *E*-ethylene bonds should result in a 4-amino-2,4-disubstituted butanoic acid residue, i.e. a γ-peptide moiety (Scheme 1). Such a species contains two chiral centers, and we have investigated the eventual asymmetrical induction due to the chiral center in **1** and **2**, the *E* or *Z*-configuration and the C-terminal acid or amide group. We have more particularly investigated the *E* and *Z*-vinylogous derivatives listed in Table 1. Single crystals of the *Z*-vinylogous *Z*-(4*S*)-



Scheme 1. Catalytic hydrogenation of vinylogous peptides **1a–d** and **2a–d** into the γ-peptides **3a–d** and **4a–d**.

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Table 1. Catalytic hydrogenation of vinylogous peptides **1a–d** and **2a–d**

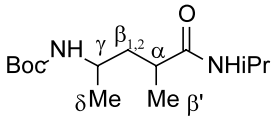
Substrates	R^1	R^2	R^3	Conditions[a]	Yield (%)[b]	γ-Peptide (*SS*/*SR*)	*de*[f]
1a	H	Me	OH	1 bar/AcOEt–CH_2Cl_2	100	**3a**/**4a** (50/50)[c]	0
1b	H	Me	NHiPr	1 bar/AcOEt–CH_2Cl_2	94	**3b**/**4b** (77/23)[d]	54
1b	H	Me	NHiPr	50 bars/AcOEt–CH_2Cl_2	97	**3b**/**4b** (82/18)[d]	64
2b	H	Me	NHiPr	1 bar/AcOEt–CH_2Cl_2	87	**3b**/**4b** (58/42)	16
1c	$(CH_2)_3$		OH	10 bars/AcOEt–CH_2Cl_2	98	**3c**/**4c** (54/46)	8
1d	$(CH_2)_3$		NHiPr	50 bars/AcOEt–CH_2Cl_2	98	**3d**/**4d** (82/18)[e]	64
2d	$(CH_2)_3$		NHiPr	50 bars/AcOEt–CH_2Cl_2	0	–	–
2d	$(CH_2)_3$		NHiPr	10 bars/MeOH	96	**3d**/**4d** (78/22)[e]	56

[a] The catalytic hydrogenation was achieved in the presence of Pd on charcoal 10%.[6]
[b] Yield in purified products.
[c] The absolute configuration of **3a** and **4a** was determined to be *SS* and *SR*, respectively, by comparison of the specific rotations with those reported in the literature.[7]
[d] The structure of **3b** was established by X-ray crystallography.
[e] The absolute configurations were assigned using ^1H and ^{13}C NMR by comparing the data of pure diastereomers **3d** and **4d** with those of **3b** and **4b**.
[f] *de* was evaluated by ^1H NMR (250 MHz) on the crude product.

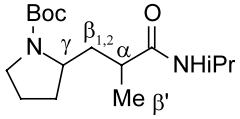
Boc-NH-CHMe-CH=CMe-CO-NHiPr **2b** and the γ-peptide (2*S*,4*S*) - Boc - NH - CHMe - CH_2 - CHMe - CO-NHiPr **3b** were submitted to X-ray diffraction,[5] and the diastereomers **3b** and **4b** were studied in solution by IR and ^1H NMR spectroscopy.

The results of the catalytic hydrogenation are listed in Table 1.[6] Vinylogous aminoacids **1a** and **1c** are easily converted with high yields into the expected γ-amino acids **3a**/**4a** and **3c**/**4c**, and vinylogous aminoamides **1b** and **1d** into **3b**/**4b** and **3d**/**4d**. The diastereoselectivity of the reaction actually depends on the structure of the substrate. No diastereoselection is observed with the vinylogous acids (*de* = 0–8%), whereas the presence of an amide group increases the *de* values (16–64%). Moreover, the configuration of the ethylenic bond has an important effect on the stereoselectivity. The higher selectivity is observed with the *E*-vinylogous aminoamides **1b** and **1d** (*de* = 64%). This can be related with the conformational preferences of the vinylogous aminoamides. The *E*-isomers adopt an extended conformation where the *Si*-side is sterically hindered by the

Table 2. ^1H NMR data for the diastereomeric molecules **3b–d** and **4b–d**



3b, **4b**



3d, **4d**

Chemical shifts (ppm)	BocNH	γ	δ	β_1	β_2	α	β′	NHiPr	ΔδBocNH	ΔδNHiPr
3b ($CDCl_3$)	4.36	3.71	1.11	1.24	1.80	2.23	1.11	6.77	2.42[a]	0.77[a]
3b (C_6D_6)	4.20	4.06	0.90	1.09	2.02	2.43	1.42	6.97		0.57[b]
3b (DMSO-d_6)	6.78	3.42	0.97	1.32	1.54	2.24	0.95	7.54		
4b ($CDCl_3$)	4.39	3.61	1.14	1.37	1.90	2.23	1.11	6.69	2.07[a]	0.87[a]
4b (C_6D_6)	4.67	3.92	1.15	1.34	2.13	2.13	1.28	5.32		2.24[b]
4b (DMSO-d_6)	6.46	3.41	1.02	1.26	1.61	2.22	0.96	7.56		
3d ($CDCl_3$)		3.92		1.27	1.57	2.30	1.07	7.47		
3d (C_6D_6)		4.19		1.05	1.82	2.63	1.27	7.77		
3d (DMSO-d_6)		3.62		1.32	1.57	2.15	0.97	7.62		

Coupling constants (Hz)	BocNH/Hγ	γ/δ	γ/β_1	γ/β_2	β_1/β_2	α/β_1	α/β_2	β′/α
3b (C_6D_6)	9.1	6.5	10.6	2.5	−13.9	2.4	11.3	6.9
3b (DMSO-d_6)	7.9	6.5	9.2	5.7	−13.4	5.9	8.9	6.9
4b (C_6D_6)	6.4	6.5	[c]	[c]	[c]	[c]	[c]	6.6
4b (DMSO-d_6)	8.3	7.2	6.6	7.8	−13.3	7.3	7.0	6.8

[a] Shift of the NH proton resonances when going from $CDCl_3$ to DMSO-d_6.
[b] Shift of the NH proton resonances when going from C_6D_6 to DMSO-d_6.
[c] The medium coupling constants could not be determined exactly, because of signal broadening. The absence of large couplings denotes a flexible molecule.

Boc group (the dihydrogen approaches predominantly by the unhindered *Re*-side), whereas the intramolecular hydrogen bond in the *Z*-isomers **2b** and **2d** results in a nearly planar conformation with 2 equiv. sides for the double bond. This conformational structure agrees with the decreasing stereoselectivity and a less efficient reduction. With **2d**, the hydrogenation failed in AcOEt–CH_2Cl_2. The use of a polar solvent such as MeOH inhibited the formation of the intramolecular interaction and promoted the reduction and consequently **3d**/**4d** was obtained with an excellent yield (96%) and an interesting diastereoselectivity (*de* = 56).

It is interesting to compare the present experimental data with those from Koskinen for the hydrogenation of the vinylogous aminoester Boc-NH-CHMe-CH=CMe-COOMe.[8] The stereoselectivity decreases according to the sequence: R^3 = NHiPr (*de* = 64%)> OMe (*de* = 33%)[8]>OH (*de* = 0%). The control of diastereoselectivity with the *E*-vinylogous derivatives can be rationalized by the concept of allylic 1,3-strain.[7] The hydrogenation occurring from the *Re*-side, and leading to the (*SS*)-isomer, is clearly the result of the addition of H_2 onto the less hindered side in a conformation of the transition state where Hγ on the stereocenter and $CH_3\beta'$ (Table 2) are eclipsed. The presence of a R^3 bulky group like NHiPr logically impedes the interconversion of the different conformers, and diastereoselection increases consequently (Scheme 1).

In the solid state, molecule **2b** assumes the same folded conformation as **2d**,[4a] and exhibits an intramolecular H-bond closing a nine-membered cycle, thus confirming the great propensity of *Z*-vinylogous residues to induce β-like folding (Fig. 1). More surprisingly, **3b** also adopts a folded structure where the carbons in Me-CH-CH_2-CH-Me define a nearly *trans–trans* planar fragment (Fig. 1). This folded structure is retained in CH_2Cl_2 and $CHCl_3$ on the basis of: (i) the presence of two NH stretchings at a low frequency (3320 cm^{-1} typical of an H-bonded NH) and at a high frequency (3433 cm^{-1} typical of a free NH); (ii) the low CO stretching frequency (1701 cm^{-1} denoting an H-bonded Boc-CO) and (iii) the small shift of the NHiPr proton resonance (0.77 ppm from $CDCl_3$ to DMSO-d_6) translating the small solvent accessibility of the NHiPr group (Table 2). In C_6D_6, a solvent which is known to spread about the proton resonances due to current ring effect, the two sets of high and small vicinal coupling constants (Table 2) confirm the *trans–trans* conformation

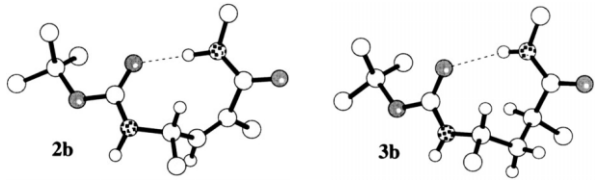


Figure 1. Crystal molecular structures of the *Z*-vinylogous peptide **2b** and the γ-peptide **3b**. The methyl hydrogens and the disordered isopropyl methyl carbons have been omitted for clarity.

of the Me-CH-CH_2-CH-Me fragment. Under the same experimental conditions, diastereomer **4b** exhibits completely different data (high frequencies of the NH stretchings at 3433 cm^{-1} and Boc-CO stretching at 1706 cm^{-1}, and the large shift of 2.24 ppm for the NHiPr proton resonance) that indicate an open extended conformation. In contrast with the *Z*-vinylogous analogue **2b** which at least partly retains a folded conformation in DMSO-d_6,[4a] both **3b** and **4b** only exhibit a very broad NH stretching absorption about 3250 cm^{-1}, indicating that DMSO solvation of the NHs is favored over the aforementioned NH···O=C H-bond. The evolution of the vicinal coupling constants (decreasing of the high values and increasing of the small values) confirms the flexibility of the molecular backbone in this strong solvating medium.[4a]

The stereoselectivity of catalytic hydrogenation of the ethylenic bond in vinylogous peptides depends both on the *Z* or *E*-configuration of the ethylene bond and the nature of the contiguous acid or ester[8] or amide group. In most cases, the stereoselectivity (*de* = 0–64%) favors the (2*S*,4*S*)-stereomer, and the best results are obtained with the *E*-ethylene bond contiguous to an amide bond. Both *Z*-vinylogous and (2*S*,4*S*)-reduced vinylogous (2*S*,4*S*-γ-peptide) motifs in a peptide chain induce a β-like folded structure stabilized by an intramolecular hydrogen bond. The stability of this turn greatly depends on the chirality since the (2*S*,4*R*)-diastereomer assumes an open structure. Recently, the mirror image of the above folded structure has been observed for (2*R*,3*R*,4*R*,5*R*,6*R*,7*R*,8*R*)-Boc-NH-CHMe-CHMe-CH-Me-CO-NH-CHMe-CHMe-CHMe-CHiPr-COOBzl, thus confirming the folding tendency of γ-peptides having the same absolute chirality in both positions 2 and 4.[9]

Acknowledgements

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5. Crystal data: **2b**: tetragonal; $P4_12_12$; $a=b=10.075(2)$ Å, $c=35.226(9)$ Å; $Z=8$, $d_{calcd}=0.978$ g cm^{-3}; 1990 reflections; $R=0.0703$ (each isopropyl methyl occupies three disordered positions) CCDC 200217. The main torsional angles: C–O–CO–NH −176°, O–CO–NH–CH 172°, CO–NH–CH–CH –76°, NH–CH–CH=C 122°, CH–CH=C–CO 0°, CH=C–CO–NH −57°, C–CO–NH–CH −178°. **3b**: tetragonal; $P4_12_12$; $a=b=9.851(1)$ Å, $c=36.762(5)$ Å; $Z=8$, $d_{calcd}=0.992$ g cm^{-3}; 1261 reflections; $R=0.0679$ (each isopropyl methyl occupies two disordered positions) CCDC 200216. The main torsional angles: C–O–CO–NH −172°, O–CO–NH–CH −173°, CO–NH–CH–CH_2 −102°, NH–CH–CH_2–CH 68°, CH–CH_2–CH–CO 71°, CH_2–CH–CO–NH −98°, CH–CO–NH–CH 179°. These data can be obtained free of charge via http://www.ccdc.cam.uk/conts/retrieving.html (or from the Cambridge Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
6. The catalytic hydrogenation was achieved in the presence of Pd on charcoal 10% for 3 days at 20°C. The resulting γ-peptides **3a–d** and **4a–d** were obtained after separation of the catalyst on Celite and chromatographic purification on a silica gel column. A graduated elution gave pure diastereomers **3** and **4**. The separation of the aminoamide diastereomers **3b**/**4b** and **3d**/**4d** was easier than for aminoacids **3a**/**4a** and **3c**/**4c**. The diastereoselectivity of hydrogenation was determined by ^{1}H NMR.
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