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Novel γ-turn mimetics with a reinforced hydrogen bond

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Abstract

Pyridylmethylphenols **2** can mimic the geometry of γ-turns. Hydrogen bonding in **2** has been characterized by X-ray crystallography, IR and NMR spectroscopy, and molecular modeling.

In addition to the frequently encountered β-turns, γ-turns are important peptide secondary structure elements.[1] While some γ-turn mimetics have been described previously,[2] none of them are based on the concept of reinforced hydrogen bonding reported here.

The characteristic feature of γ-turns **1** is a seven-membered, hydrogen bonded ring. In small, linear peptides such a hydrogen bond is not sufficient to constrain the conformation of the peptide in solution. Our design effort targeted towards reinforcing the hydrogen bond and resulted in **2** with a phenol–pyridine hydrogen bond (Scheme 1).

We prepared selected examples of **2** corresponding to tripeptides Val-Gly-Ser (mimetic **5**) and Val-Gly-Ala (mimetic **7**), in addition to compound **6** used in structural studies. Our synthetic strategy involved ketone **4** as the key intermediate, allowing the introduction of R_{i+1} substituents, if desired. Ketone **4** was synthesized via *ortho*-lithiation[3] of **3** and coupling with 6-chlorocarbonyl-2-pyridinecarboxylic acid methyl ester.[4] Reduction with $NaBH_4$, aqueous acidic hydrolysis of the MOM group and hydrogenolysis in TFA/CH_2Cl_2 over Pd/C yielded **5**, **6** and **7** as a mixture, which was separated by MPLC.[5] We also prepared the parent molecule **8** (Table 1) as a reference compound via a literature route.[6]

We carried out structural studies of **5–8** both in solution and in the solid state. According to the IR spectra (Table 1), **7** and **8** are unambiguously and fully hydrogen bonded in chlorinated hydrocarbons. Based on a comparative analysis of the spectra, the free OH signals in **5** and **6** are assigned to the aliphatic hydroxyls, suggesting **5** and **6** are fully hydrogen bonded as well. The NMR chemical shifts (Table 1) are also consistent with hydrogen bonding, with slightly weaker hydrogen bonds in **5** and **6** than in **7** and **8**.

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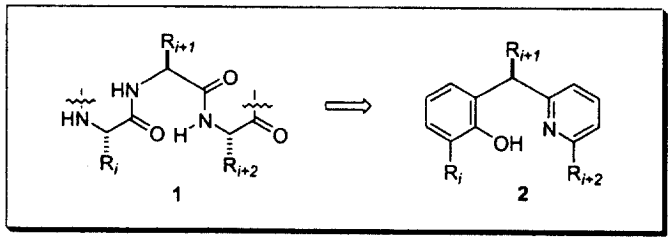
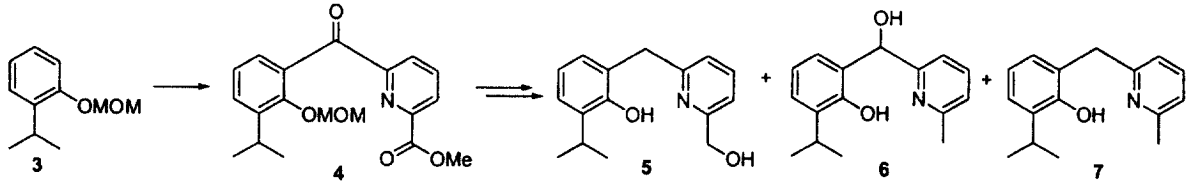


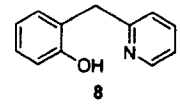


Scheme 1.

Table 1

Hydrogen bonding in IR and NMR. The presence (+) or absence (−) of signals in IR is indicated

	5	6	7	8
IR[a]				
C_{ar}-OH···N	+	+	+	+
Free C_{ar}-OH	-	-	-	-
Free C-OH	+	+	-	-
^{1}H NMR[b]				
C_{ar}OH δ($CDCl_3$)	11.2	10.9	12.0	11.7



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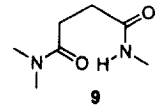


9

[a]Dilute (<10 mM) CCl_4 solutions. 2-*i*-Pr-phenol is not intermolecularly hydrogen bonding even in 100 mM solution. [b]From routine ^{1}H NMR spectra. The OH signal of 2-*i*-Pr-phenol resonates at δ4.65 - 4.70 in 1-100 mM solution.

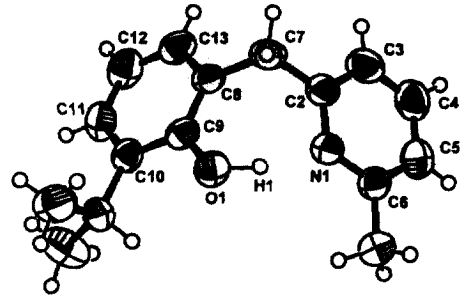
Overall, it appears that **5–8** all have a high preference for the hydrogen bonded conformation in solution. In comparison, **9** (Table 1) was only partially hydrogen bonded under comparable conditions.[7]

We also obtained theoretical estimates of the strength of the hydrogen bond in **7** from molecular dynamics simulations. We carried out fully converged simulations using the Mixed Mode Monte Carlo/Stochastic Dynamics protocol,[8] also reported in connection with **9**.[9] Thus, at 295K **7** is 92–99% hydrogen bonded,[10] while **9** has been reported to be only 40% hydrogen bonded.[9] Consequently, both theoretical and experimental structural studies in solution support the conclusion that we have successfully reinforced the hydrogen bond upon converting **1** to **2** and that the hydrogen bond in **2** can act as a conformational lock.

The geometries of the hydrogen bonded conformations were obtained from X-ray crystallographic studies. According to X-ray diffraction,[11] **6** and **7** adopt intramolecularly hydrogen bonded conformations in the solid state, with two enantiomeric conformations present in the crystal of **7**.[12] The O···N distance in **6** and **7** is 2.69–2.70 Å (Table 2), resulting in an (O)H···N distance of 1.7 Å. In comparison, a range of 1.7–2.2 Å has been observed for typical (O)H···N hydrogen bonds in crystals.[13] The corresponding mean distances in phenol–pyridine hydrogen bonding are 2.0 and 2.2 Å in inter- and intramolecular cases, respectively.[14] Short intramolecular hydrogen bonds (down to 1.63 Å) have been recorded in 2-(2-pyridyl)phenols, with six-membered hydrogen bonded rings.[14] However, seven-

Table 2
Geometric parameters in the crystal structures of **6** and **7**. Conformer A of **7** is illustrated

Parameter	Definition	6	7, conf A	7, conf B
O···N (Å)	O1-N1	2.702(4)	2.690(4)	2.698(4)
(O)H···N (Å)	H1-N1	1.65(5)	1.71(4)	1.69(4)
<DHA (deg)	O1-H1-N1	159(2)	157(2)	159(2)
<HAB (deg)	H1-N1-C4	169(2)	165(2)	164(2)
<Angle3 (deg)	N1-O1-C9	93.7(4)	96.9(4)	57.0(4)
<Angle4 (deg)	C4-N1-O1	160.5(4)	157.1(4)	157.3(4)
ϕ' (deg)	C2-C7-C8-C9	-80.3(4)	71.8(4)	-72.9(4)
φ' (deg)	N1-C2-C7-C8	62.7(4)	-65.3(4)	65.3(4)



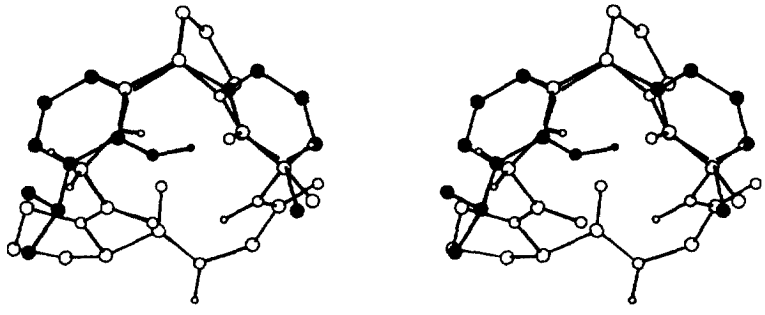


Figure 1. Stereo view of the crystal structure of **7** (dark) superimposed with the crystal structure of cyclo-(Gly-Pro-Gly-D-Ala-Pro) (white spheres).[15] The (C=)O···(H-)N distance in the γ-turn is 2.92 Å

membered, intramolecularly hydrogen bonded phenol–pyridine rings have not been described previously. Overall, the structural details from X-ray diffraction — the practically linear hydrogen bond geometry (Table 2) and the short (O)H···N distance — are consistent with relatively strong hydrogen bonding in **2**.

The geometric properties of the conformers of **6** and **7** (Table 2) mimic those of γ-turns. Firstly, the torsion angles ϕ' and φ' fall into the ϕ,φ range usually found in classic γ-turns (70–95°, –75–45°) and in inverse γ-turns (–95–70°, 45–40°).[1] Secondly, the superimposition of **7** and the γ-turn in cyclo-(Gly-Pro-Gly-D-Ala-Pro) (Fig. 1)[15] reveals a good fit, with a superimposition RMSD of 0.21 Å between the backbone atoms and the corresponding atoms in **7**. Additionally, in this particular case the side chains (or potential side side chains) of *i* and *i*+3 residues of the γ-turn in the cyclic peptide coincide well with the *i*-Pr and Me substituents of **7**. Thus, the comparison suggests that mimetics **2** are capable of orienting side chains as found in peptides.[16]

In conclusion, we have designed peptide turn mimetics **2** where the hydrogen bond of γ-turns has been replaced by a stronger one. Structural studies confirm that the hydrogen bond has been successfully reinforced and that **2** can mimic the geometry of γ-turns. Mimetics **2** provide a potential scaffold for biological applications where a 'soft' conformational lock and possibility of slight adjustment of geometry upon binding may be advantageous. Additionally, **2** can be used in evaluating molecular modeling methods, and our studies in this field will be reported in due course.

Acknowledgements

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4. The by-products from overaddition could easily be removed by crystallization after $NaBH_4$ reduction and MOM hydrolysis. Thus, although we tested stannylation of *ortho*-lithiated **3** and Stille coupling with the acid chloride to afford ketone **4**, Stille coupling was not a superior approach in our case.
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10. AMBER* force field (united atom, hydrogens on aromatic carbons) (92% hydrogen bonding) or MMFF force field (99% hydrogen bonding), employing the GB/SA continuum $CHCl_3$ model. The values were obtained from 1 ns MC/SD simulations at 295K carried out in a MacroModel 6.0. We employed the convergence criteria described by McDonald and Still, Ref. 9. The hydrogen bonding criteria are adapted from Ref. 9. Simulation data for compound **9** has been obtained using united atom AMBER* (Ref. 9).
11. Crystal Data: **6**: monoclinic, space group *P21/n* (no. 14), a=9.169(2), b=7.963(2), c=19.679(3) Å, β=91.35(2)°, V=1436.5(5) Å^3, Z=4, 2040 reflections, $R1$=0.0605 and w$R2$=0.1370 for 1901 unique data with $I>2\sigma(I)$ and $R1$=0.1032, w$R2$=0.1516 for all data and for 183 parameters; **7**: monoclinic, space group *P21/a* (no. 14), a=15.978(2), b=7.779(2), c=23.696(3) Å, β=109.57(2)°, V=2775.2(9) Å^3, F(000)=1112, 3845 reflections, $R1$=0.0510 and w$R2$=0.1183 for 3677 unique data with $I>2\sigma(I)$ and $R1$=0.1038, w$R2$=0.1368 for all data and for 340 parameters. The full details have been deposited to CCDC under deposition numbers 121736 and 121737.
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16. It should be noted that γ-turns themselves are not sufficient to constrain the orientation of the i and i+3 side chains, and additional conformational constraints, such as cyclization, may be necessary.