Supporting Information

Sequence dependent folding motifs of the secondary structures of Gly-Pro and Pro-Gly containing oligopeptides

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1. Synthesis procedures and characterization of the peptides

1.1 Synthesis method

Both the peptides Boc-^DPro-Gly-NHBn-OMe and Boc-Gly-^DPro-NHBn-OMe were synthesized by standard synthetic procedure reported in the literature.¹

Synthetic procedure of Boc-D-Pro-Gly-NHBn-OMe: Commercially available Boc-D-Pro-COOH was coupled with N-Hydroxysuccinimide (NHS) in the presence of N,N'-Dicyclohexylcarbodiimide (DCC), tetrahydrofuran (THF) in a round bottom flask kept at ice condition and left at room temperature for 12 h. The product was then coupled with Glycine in the presence of NaHCO₃, THF and then acidified with 10% HCl and this resulted the formation of Boc-^DPro-Gly-OH. Boc-^DPro-Gly-OH was then mixed with 4-Methoxybenzylamine in the presence of EDC.HCl, HOBt, DIPEA, and DMF at 0^o C. The final product was received after 12 hours of reaction at room temperature. The final compound was purified by column chromatography using ethyl acetate and hexane as solvent in 65% yield. Synthetic procedure has been shown also in the Figure S1 provided below.



Figure S1. Synthetic Scheme of Boc-^DPro-Gly-NHBn-OMe

Synthetic procedure of Boc-Gly-^DPro-NHBn-OMe: Commercially available Boc-Gly-COOH was coupled with N-Hydroxysuccinimide (NHS) in the presence of N, N'-Dicyclohexylcarbodiimide (DCC), tetrahydrofuran (THF) in a round bottom flask kept at ice condition and then left at room temperature for 12 h. The product was then coupled with the Boc-^DPro-OH in the presence of NaHCO₃, THF and then acidified with 10% HCl and this resulted the formation of Boc-Gly-^DPro-OH. The product Boc-Gly-^DPro-OH was then coupled with 4-Methoxybenzylamine in the presence of EDC.HCl, HOBt, DIPEA, DMF at 0^o C. Afterwards, the reaction was maintained at room temperature and kept for 12 hours with continuation of the stirring. The final compound was purified by column chromatography using ethyl acetate and hexane as solvent in 72% yield. The synthetic procedure has also been depicted in Figure S2 provided below.



Figure S2. Synthetic Scheme of Boc-Gly-^DPro-NHBn-OMe.

1.2 ¹H NMR Characterization

¹H NMR of Boc-^DPro-Gly-NHBn-OMe (400 MHz, CDCl₃, 298.15 K): δ 6.80-7.50 (m,6H, NH_{Gly}, NH_{NHBn}, CH^{Ar}) 3.4-4.5 (m, 10H, CH_{Gly}, OCH₃, CH_{NHBn}, CH_{Pro}) 1.8-2.2 (m,4H, CH_{Pro})
 1.37 (s, 9H, CH_{Boc})

¹**H NMR of Boc-Gly-^DPro-NHBn-OMe** (400 MHz, CDCl₃, 298.15 K): δ 6.80-7.50 (m,5H, NH_{NHBn}, CH^{Ar}), 5.37(s, 1H, NH_{Gly}) 3.4-4.5 (m, 10H, CH_{Gly}, OCH₃, CH_{NHBn}, CH_{Pro}) 1.8-2.2 (m,4H, CH_{Pro}) 1.43 (s, 9H, CH_{Boc})





Figure S4. ¹H NMR spectrum of Boc-^DPro-Gly-NHBn-OMe recorded in CDCl₃ solvent.



1.3 HRMS spectra of peptides

Figure S5. HRMS mass spectrum of Boc-^DPro-Gly-NHBn-OMe.



Figure S6. HRMS mass spectrum of Boc-Gly-^DPro-NHBn-OMe.

2. Solution phase Spectroscopy methods

2.1. Solution phase IR spectroscopy.

Solution phase IR spectra of Boc-Gly-^DPro-NHBn-OMe and Boc-^DPro-Gly-NHBn-OMe peptides were measured at 293 K using Fourier-Transform IR spectrometer (Bruker Vertex 70). To record the IR spectra, the peptides are dissolved in $CDCl_3$ solvent and the concentration of the peptide solutions were maintained at 8 mM. The peptide solutions were put in a cell of 1 mm path length consisting of CaF_2 windows.

2.2. Solution phase NMR spectroscopy.

Both 1D and 2D ¹H NMR spectra of Boc-Gly-^DPro-NHBn-OMe and Boc-^DPro-Gly-NHBn-OMe peptides were measured in CDCl₃ solvent using a 400 MHz NMR spectrometer (Bruker-400). 1D ¹H NMR spectra were measured in CDCl₃ for characterization of the peptides synthesized in this work.

2.3. 2D-NMR spectroscopy.

Rotating frame Overhauser SpectroscopY (ROESY) of the two peptides were performed in CDCl₃ solvent using a 400 MHz NMR spectrometer (Bruker-400). The ROESY spectra reveal the correlations between the protons that are separated by few bonds but are spatially close. These spectra are useful to determine the structures of different conformers of the peptides.

2.4. NMR titration.

NMR titration with DMSO-d₆ by probing the chemical shift positions of the N-H groups in the peptides is performed to determine whether the N-H group is free or intramolecular hydrogen bonded. The chemical shift positions of the N-H groups were monitored by successive addition of 5 μ L DMSO-d₆ in the CDCl₃ solution of the peptides. If there is significant downfield chemical shift or deshielding of the N-H proton by addition of DMSO-d₆, the N-H group in the

peptide is free and involved in intermolecular hydrogen bonding with DMSO. On the other hand, the change in the chemical shift of the N-H proton will be minimal or negligible on addition of DMSO-d₆ if the N-H group is already involved in intramolecular hydrogen bonding in the peptide.



Figure S7. NMR titration of Boc-Gly-^DPro-NHBn-OMe in $CDCl_3$ with stepwise addition of DMSO-d₆ by monitoring the chemical shift positions of the Gly and Bn N-H protons.



Figure S8. NMR titration of Boc-^DPro-Gly-NHBn-OMe in CDCl₃ with stepwise addition of DMSO-d₆ by monitoring the chemical shift positions of the Gly and Bn N-H protons.

DMSO-d6 titration of Boc-Gly-^DPro-NHBN-OMe sequence shows both NH are involved in intra-molecular hydrogen bond as chemical shift of both the NH upon addition of DMSO-d6 is very minimal.

In the case of Boc-^DPro-Gly-NHBn-OMe glycine NH shows very less chemical shift compared to NHBn NH upon addition of DMSO-d6. It shows that in solution glycine NH is free whereas NHBn NH is involved in hydrogen bonding.

3. Gas phase spectroscopy methods.

The peptide molecules were brought into the vapor phase without any fragmentation using a laser desorption technique, which has been described in detail elsewhere.² A homogeneous mixture (2:1) of the peptide and graphite powder (Sigma Aldrich, size ~ 20 microns) was pressed in a hydraulic press with 2-3 tons of pressure to prepare a pellet of 6 mm diameter and 2 mm thickness. The pellet was put in a sample holder connected with a motorized assembly which was mounted with the vacuum chamber. The sample pellet was placed near the pulse valve in such a manner that it was away from the axis of the molecular beam by ~ 2 mm while the side edge of the pellet was maintained at a distance of ~ 1 mm from the face plate of the pulse valve. Second harmonic output (~ 0.6-0.7 mJ at 532 nm) of a Nd:YAG laser (Continuum, Minilite-I, 10 Hz, 10 ns) was mildly focused on the surface of the pellet which was near the pulse valve so that the desorption happened within 2-3 mm from the orifice of the pulse valve. The sample pellet was rotated at a speed of 0.5 mm/sec to avail the fresh spot of the pellet surface.

The desorbed peptide molecules were enrouted in the supersonic expansion of Ar (~5 bar) carrier gas and internally cooled through enormous collision with carrier gas near the valve orifice. The cold peptide molecules were ionized by second harmonic output (0.2–0.3 mJ) of a tunable dye laser (ND6000, Continuum) pumped by frequency doubled output of an Nd:YAG laser (10 nanoseconds, 10 Hz, Surelite II-10, Continuum) and the ions were analyzed in the TOF mass spectrometer (Jordan TOF, USA). The details of the experimental setup were described elsewhere.^{3,4}

Mass-selected electronic spectra of the peptides were recorded by scanning the UV laser using one-color resonant 2-photon ionization (1C-R2PI) method. In this technique, the first photon of the laser excites the molecules to the first excited electronic state (S_1) while the second photon of the laser at the same wavelength ionizes the molecules. UV-UV hole-burning spectroscopy was used to determine the presence of different conformers of the peptide in the experiment. In this method, one of the UV lasers (probe laser, 10 ns, 10 Hz, ND6000, Continuum) was fixed at the wavelength of one of the electronic bands in the R2PI spectrum and another pump UV laser (10 ns, 10 Hz, ND6000, Continuum) fired ~ 150 ns prior to the probe laser scanned in the region of the electronic spectrum. Both the lasers were in the counterpropagating direction and intersecting the molecular beam in the mutually perpendicular fashion. The depletion of the ion signal of the probe laser beam is observed due to the R2PI bands which belong to the same conformer of the peptide. The IR spectra of the peptides were measured using resonant ion-dip infrared spectroscopy (RIDIRS). In the RIDIRS, the UV laser wavelength was fixed at one of the electronic bands of a conformer and the IR laser preceding the UV laser by ~100 was tuned in the region of the N-H stretching region of the peptide. The IR spectra were obtained as a depletion in the ion signal when the IR laser frequency was matching with the vibrational frequency of the molecules. Finally, IR-UV hole-burning spectroscopy was used to determine the presence of different conformers of the peptide in the experiment. In this technique, the IR laser wavelength was fixed at one of the N-H frequencies of the peptides and the UV laser fired ~100 ns after the UV laser was scanned in the whole electronic spectral region of the peptide. The depletion in the UV ion signal is obtained for the R2PI bands arises from the same conformer. A tunable IR laser (Laser Vision, pulse energy ~ 4-5 mJ, resolution ~ 2.5 cm⁻¹) based on optical parametric oscillator (OPO)/ optical parametric amplifier (OPA) pumped by an unseeded Nd: YAG laser (Continuum, Surelite II-10, 10 nanoseconds, 10 Hz) was used for the IR-UV double resonance experiment.

4. Conformational search, calculated structures, relative energies, and vibrational frequencies of the lowest energy conformers of both the peptides and benchmarking of the DFT functionals

4.1. Conformational search for Boc-Gly-^DPro-NHBn-OMe and Boc-^DPro-Gly-NHBn-OMe peptides

4.1.1. Flowchart of process of conformational selection

The following flowchart describes the detailed conformational search using MMFF94 force field calculation as well as chemical intuition followed by quantum chemistry calculations of a large set of conformers at the HF/6-31G(d), M05-2X/6-31+G(d), B3LYP-D3/def2-TZVPP, B97-D3/def2-TZVPP, ω B97X-D/def2-TZVPP, and M06-2X/6-311++G(2d,2p) levels of theory. In fact, M05-2X, B3LYP-D3, B97-D3, and ω B97X-D level calculations are done for the Gly-Pro peptide for 68 structures up to energy ~ 25 kJ/mol while the same is done for the Pro-Gly peptide for 52 structures up to ~ 16 kJ/mol. Finally, M06-2X/6-311++G(2d,2p) level calculations are done for the same has been done for the Pro-Gly peptide for 16 structures up to energy ~ 8 kJ/mol.



Figure S9. Conformational search procedure for Gly-Pro and Pro-Gly sequences using a combination of molecular mechanics and manual search methods.

4.1.2. Dihedral angles used for manual generation of the conformers of the Gly-Pro and Pro-Gly peptides



Figure S10. Conformers named based on (a) C7 D&L orientation (b) Bz group orientation and (c) OMe group orientation.

4.2. Performance of B3LYP-D3/def2-TZVPP, B97-D3/def2-TZVPP, ωB97X-D/def2-TZVPP, and M06-2X/6-311++G(2d,2p) in predicting energetics and IR frequencies of the observed conformers of the peptides in the experiment

The numbering of the conformers of the peptides (GP1....GPn or PG1....PGn) in terms of energy ranking is done at the M06-2X/6-311++G(2d,2p) level of theory as this level of calculation does better job in terms of the assignment of the observed conformers of both the peptides. The same numbered conformers are simply used for calculations of the energies and frequencies at other levels of DFT.



4.2.1. Energy landscapes of Gly-Pro peptide at different levels of theory

Figure S11. Energy landscape of a few low energy conformers of (a) Boc-Gly-^DPro-NHBn-OMe calculated at 300 K at the M06-2X/6-311++G(2d,2p) level of theory. The color coded conformers are the predicted ones observed in the experiment. See the main text for the nomenclature.



Figure S12. Structures of the 16 lowest energy conformers of Boc-Gly-^DPro-NHBn-OMe optimized at the M06-2X/6-311++G(2d,2p) level of theory. The color coded conformers are the predicted ones observed in the experiment.



Figure S13. Energy landscape of Boc-Gly-^DPro-NHBn-OMe showing Gibbs free energies (ΔG_{rel}) relative to the most stable conformer calculated at 300 K at the B3LYP-D3/def2-TZVPP level of theory. The label C5-C7_D is used thrice merely to show the close-lying energy levels in a distinct manner. See the main text for the nomenclature.



Figure S14. Energy landscape of Boc-Gly-^DPro-NHBn-OMe showing Gibbs free energies (ΔG_{rel}) relative to the most stable conformer calculated at 300 K at the B97-D3/def2-TZVPP level of theory. The label C5-C7_D is used thrice merely to show the close-lying energy levels in a distinct manner. See the main text for the nomenclature.



Figure S15. Energetic diagram of Boc-Gly-^DPro-NHBn-OMe showing Gibbs free energies (ΔG_{rel}) relative to the most stable conformer at 300 K after calculation at ω B97X-D/def2TZVPP level of theory. The label C5-C7_D is used thrice merely to show the close-lying energy levels in a distinct manner. See the main text for the nomenclature.



4.2.2. Energy landscapes of Pro-Gly peptide at different levels of theory

Figure S16. Energy landscape of a few low energy conformers of (a) Boc-^DPro- Gly-NHBn-OMe calculated at 300 K at the M06-2X/6-311++G(2d,2p) level of theory. See the main text for the nomenclature. The color coded conformers are the predicted ones observed in the experiment.



Figure S17. Structures of the 16 lowest energy conformers of Boc-^DPro-Gly-NHBn-OMe optimized at the M06-2X/6-311++G(2d,2p) level of theory. The color coded conformers are the predicted ones observed in the experiment.



Figure S18. Energy landscape of Boc-^DPro-Gly-NHBn-OMe showing Gibbs free energies (ΔG_{rel}) relative to the most stable conformer calculated at 300 K at the B3LYP-D3/def2-TZVPP level of theory. The labels C7_D-C7_L and F-C10,are used twice merely to show the close-lying energy levels in a distinct manner. See the main text for the nomenclature.



Figure S19. Energy landscape of Boc-^DPro-Gly-NHBn-OMe showing Gibbs free energies (ΔG_{rel}) relative to the most stable conformer at 300 K after calculation at B97-D3/def2TZVPP level of theory. The labels C7_D-C7_L and F-C10 are used twice merely to show the close-lying energy levels in a distinct manner.



Figure S20. Energy landscape of Boc-^DPro-Gly-NHBn-OMe showing Gibbs free energies (ΔG_{rel}) relative to the most stable conformer calculated at 300 at ω B97X-D/def2TZVPP level of theory. The labels C7_D-C7_L and F-C10 are used twice merely to show the close-lying energy levels in a distinct manner.

4.2.3 Comparison of the theoretical IR NH stretching frequencies with those observed in

the experiment

In comparing the IR predictions using various functionals, we restrict to the conformers having energies less than 14 kJ/mol for Gly-Pro and 7 kJ/mol for Pro-Gly.

Conf. A Conf. B	3322		~~~~~~	3437	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Conf. C	3313	~~~~~~		34	50
GP1-C5-C7 _D -9 ⁻ -c	3324	3355		3445 3446	∆G _{rel} = 0.00 kJ/mol
GP2-C5-C7 _D -g ⁻ -t		3357		3450	∆ <i>G</i> _{rel} = 1.14 kJ/mol
GP3-C5-C7 _D -g⁻-t		3362		3442	∆G _{rel} = 1.45 kJ/mol
GP4-C5-C7 _{D^{-g⁻-c}}		3362		3442	∆G _{rel} = 1.45 kJ/mol
GP5-C5-C7 _D -9⁻-t		3356		3451	∆ <i>G</i> _{rel} = 1.67 kJ/mol
GP6-C5-C7 _D -g [⁺] -c			3389	3461	$\Delta G_{\rm rel}$ = 3.48 kJ/mol
GP7-C5-C7 _D -g [⁺] -t			3385	3461	$\Delta G_{\rm rel}$ = 3.60 kJ/mol
GP8-C5-C7 _{D^{-g⁺}-t}			3385	3465	∆G _{rel} = 3.82 kJ/mol
GP9-C5-C7 _D -g [⁺] -c			3386	3461	$\Delta G_{\rm rel}$ = 4.49 kJ/mol
GP10-C5-C7 _D -g⁻-(•	337	70	3453	∆ <i>G</i> _{rel} = 7.98 kJ/mol
GP11-F-C10-g [⁺] -t			3403		3490 ∆G _{rei} = 8.47 kJ/mol
GP12-F-C7 _D -g⁻-t		3368	3	3421	$\Delta G_{\rm rel}$ = 9.94 kJ/mol
GP13-F-C10-g [⁺] -t			3400		3488 _ ∆G _{rel} = 10.81 kJ/mo
GP14-F-C7 _D -g⁻-c		3369	9 34	10	∆G _{rel} = 11.32 kJ/mol
GP15-F-C10-g⁻-c			3421	3468	∆ <i>G</i> _{rel} = 11.75 kJ/mol
GP16-C5-C7 _D -g⁻-t		3358		3443	∆ <i>G</i> _{rel} = 13.44 kJ/mol
		<u> </u>		<u> </u>	
50 330	0 33		3400 Ivenumber (3450 cm ⁻¹)	3500 3

4.2.3.1 Gly-Pro IR NH results and comparison to experiment

Figure S21. Comparison of the experimental IR spectra with the theoretical IR spectra of the sixteen low energy conformers of Boc-Gly-^DPro-NHBn-OMe calculated at the M06-2X/6-311++G(2d,2p) level of theory. Scaling has been done by taking Z-Gly-OH molecule as reference. Scaling factor is 0.948 at this particular level of theory. The theoretical stick spectra, which are color coded, are the predicted structures for the three observed conformers in the experiment.

Conf. A	3322	3437	
Conf. C	3313	3450	
GP3-C5-C7 _D -g ⁻ -t	3324 3343	3443 3446	$\Delta G_{\rm rel} = 0.00 \rm kJ/mol$
GP4-C5-C7 _D -g ⁻ -c	3343	3443	∆G _{rel} = 0.01 kJ/mol
GP7-C5-C7 _D -g [⁺] -t	3349	3459	∆G _{rei} = 1.35 kJ/mol
GP2-C5-C7 _D -g ⁻ -t	3349	3459	∆G _{rel} = 1.36 kJ/mol
GP5-C5-C7 _{D^{-g⁻-t}}	3348	3459	∆G _{rel} = 1.36 kJ/mol
GP6-C5-C7 _D -9 [⁺] -c	3368	3465	$\Delta G_{\rm rel} = 5.77 \rm kJ/mol$
GP8-C5-C7 _D -g [⁺] -t	3368	3465	$\Delta G_{\rm rel}$ = 5.81 kJ/mol
GP1-C5-C7 _D -9 ⁻ -с	3355	3447	∆G _{rel} = 5.95 kJ/mol
GP9-C5-C7 _D -g [⁺] -c	3368	3465	∆ G _{rel} = 6.08 kJ/mol
GP11-F-C10₋g [⁺] -t	Ľ	3421 ∆G _{rel} = 6.74 k	J/mol 3501
GP10-C5-C7 _{D^{-g⁻}-c}	3362	3462	$\Delta G_{\rm rel}$ = 6.56 kJ/mol
GP12-F-C7 _D -g⁻-t	3349	3422	∆ <i>G</i> _{rel} = 6.53 kJ/mo
GP14-F-C7 _{p⁻g} ⁻-c	3349	3422	$\Lambda G_{\rm rel} = 6.74 \rm kJ/mol$
GP15-F-C10-g⁻-c		3433	3491 _ ∆G _{rel} = 7.84 kJ/mol
GP13-F-C10-g [⁺] -t	$\Delta G_{\rm rel}$ = 9.88 kJ/mol	3433	3496
GP16-C5-C7 _D -g⁻-t	3344	3456	∆G _{rel} = 10.07 kJ/mol
50 3300	3350 Wave	3400 - 3450 number (cm ⁻¹)	3500 35

Figure S22. Comparison of the experimental IR spectra with the theoretical IR spectra of the sixteen low energy conformers of Boc-Gly-^DPro-NHBn-OMe calculated at the B3LYP-D3/def2-TZVPP level of theory. Scaling has been done by taking Z-Gly-OH molecule as reference. Scaling factor is 0.958 at this particular level of theory.

Conf. A	3322	3437	
Conf. B	3313	345	0
Conf. C	3324	3446	
GP3-C5-C7 _D -g-t	3330	3436	∆ <i>G</i> _{rel} = 0.00 kJ/mo
GP4-C5-C7 _D -g ⁻ -c	3330	3436	$\Delta G_{\rm rel} = 0.00 \text{ kJ/mo}$
GP9-C5-C7 _p -g [*] -c	3357	3460	∆G _{rel} = 1.38 kJ/mo
GP7-C5-C7 _D -g [⁺] -t	3334	3455	∆G _{rel} = 2.53 kJ/mo
GP5-C5-C7 _{D-9} t	3334	3455	$\Delta G_{\rm rel}$ = 2.59 kJ/mo
GP2-C5-C7 _D -g ⁻ -t	3334	3454	∆G _{rei} = 2.66 kJ/mo
GP6-C5-C7 _D -g [⁺] -c	3360	3460	∆G _{r0l} = 2.79 kJ/mo
GP8-C5-C7 _D -g [⁺] -t	3360	3460	∆G _{rel} = 2.79 kJ/mo
GP1-C5-C7 _D -g ⁻ -c	3339	, 3443	∆G _{rel} = 4.34 kJ/mo
GP14-F-C7 _D -9 [−] -c	3335	3409	∆G _{rel} = 4.42 kJ/mo
GP12-F-C7 _D -g ⁻ -t	3335	3409	∆G _{rel} = 4.43 kJ/mo
GP10-C5-C7 _D -g ⁻ -c	3350	3459	∆G _{rel} = 6.90 kJ/mol
GP11-F-C10-g [*] -t		3421	3497 ∆G _{rei} = 6.97 kJ/mo
GP15-F-C10-g c		3430	3486 $\Delta G_{\rm rol} = 7.55 \rm kJ/mol$
GP16-C5-C7 _D -g ⁻ -t	3326	3456	∆G _{rei} = 8.75 kJ/mo
GP13-F-C10-g-t		3419	3496 AG _{rel} = 9.40 kJ/mo
50 3300	3350 Wa	3400 3450 venumber (cm ⁻¹)	3500 3

Figure S23. Comparison of the experimental IR spectra with the theoretical IR spectra of the sixteen low energy conformers of Boc-Gly-^DPro-NHBn-OMe calculated at the B97-D3/def2-TZVPP level of theory. Scaling has been done by taking Z-Gly-OH molecule as reference. Scaling factor is 0.975 at this particular level of theory.

Conf. A	3322			3437V		
Conf. B	3313	~~~~~	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	3450	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	~
Conf. C	3324			mm 2	146	~
GP4-C5-C7 _D -g ⁻ -C		3343		3446		0.00 kJ/mo
GP3-C5-C7 _D -g ⁻ -t	1	3343		3446	∆ G _{rel} =	0.03 kJ/mol
GP7-C5-C7 _D -g [⁺] -t	L:	3343		3457	∆ G _{rel} =	1.54 kJ/mol
GP5-C5-C7 _D -g ⁻ -t	13	3343		3457	∆ G _{rel} =	1.75 kJ/mol
GP2-C5-C7 _D -g ⁻ -t	1	3343		3457	∆ G _{rel} =	2.15 kJ/mo
GP9-C5-C7 _D -g ⁺ -C		8	3375	346	$6 \int \Delta G_{rel} =$	5.71 kJ/mol
GP11-F-C10-g [⁺] -t			3405	∆ G _{rel} = 7.4	0 kJ/mol	3507
GP1-C5-C7 _D -g ⁻ -C		33	58	3446	∆ G _{rel} =	7.45 kJ/mo
GP12-F-C7 _D -g⁻-t		³³⁵²		³⁴¹⁸	∆ G _{rel} =	8.94 kJ/mo
GP14-F-C7 _D -g [–] -C		3352		3418	∆ G _{rel} =	8.94 kJ/mo
GP8-C5-C7 _D -g [⁺] -t			3376	3463	∆ G _{rel} =	9.02 kJ/mo
GP6-C5-C7 _D -g [⁺] -C			3376	3464	∆ G _{rel} =	9.07 kJ/mo
GP16-C5-C7 _D -g ⁻ -1	: 1	3345	0.6	3454	$\Delta \mathbf{G}_{rel} = \mathbf{f}$	10.46 kJ/mo
GP13-F-C10-g [⁺] -t			3402	∆ G _{rel} = 10.	.71 kJ/mol	3506
GP10-C5-C7 _D -g ⁻ -(;	3359)	3461	∆G _{rel} = '	l1.83 kJ/mo
GP15-F-C10-g ⁻ -C	∆ G _{rel}	= 14.36	kJ/mol 3	3406	3488	
50 3300		 350	3400	3450	3500	3:

Figure S24. Comparison of the experimental IR spectra with the theoretical IR spectra of the twelve low energy conformers of Boc-Gly-^DPro-NHBn-OMe calculated at the ω B97X-D/def2-TZVPP level of theory. Scaling has been done by taking Z-Gly-OH molecule as reference. Scaling factor is 0.945 at this particular level of theory.

4.2.3.2. Gly-Pro unscaled and scaled NH frequencies for M06-2X/6-311++G(2d,2p)

Table S1. Harmonic and scaled NH stretching frequencies of 16 low energy conformers of Boc-Gly-^DPro-NHBn-OMe peptide calculated at the M06-2X/6-311++G(2d,2p) level of theory. Determination of the scaling factor for the N-H stretching frequency has been shown below the table.^{a,b}

^aThe scaling factor for the N-H stretching frequencies of both the peptides was derived using the experimental N-H stretching frequency of Z-Gly-OH peptide reported in the literature.⁵ The scaling factor for this particular level of theory i.e. M06-2X/6-311++G(2d,2p) was obtained when the experimental NH frequency of Z-Gly-OH was divided by the theoretical harmonic NH frequency calculated at the same level of theory. The reported experimental NH stretching

	Glycine _{NH}	(cm ⁻¹)	NHBn _N	$H(cm^{-1})$
Conformers	Harmonic	Scaled	Harmonic	Scaled
	ν_{N-H}	ν_{N-H}	V _{N-H}	ν_{N-H}
GP1-C5-C7 _D -g ⁻ c	3633	3445	3539	3355
GP2-C5-C7 _D -g-t	3637	3450	3541	3357
GP3-C5-C7 _D -g ⁻ -	3631	3442	3546	3362
GP4-C5-C7 _D -g-c	3631	3442	3547	3362
GP5-C5-C7 _D -g-t	3640	3451	3541	3356
$GP6-C5-C7_D-g^+-c$	3651	3461	3575	3389
GP7-C5-C7 _D -g ⁺ -t	3651	3461	3570	3385
GP8-C5-C7D-g ⁺ -t	3655	3465	3571	3385
$GP9-C5-C7_D-g^+-c$	3651	3461	3571	3386
GP10-C5-C7 _D -g ⁻ -c	3643	3453	3555	3370
GP11-F-C10-g ⁺ -t	3681	3490	3589	3403
GP12-F-C7 _D -g-t	3609	3421	3553	3368
GP13-F-C10-g ⁺ -t	3679	3488	3587	3400
GP14-F-C7 _D -g ⁻ -c	3597	3410	3553	3369
GP15-F-C10-g⁻-c	3658	3468	3608	3421
GP16-C5-C7 _D -g ⁻ -t	3632	3443	3542	3358

frequency for the Z-Gly-OH peptide is 3472 cm⁻¹ whereas the theoretical harmonic NH

stretching frequency calculated at the M06-2X/6-311++G(2d,2p) level of theory is 3661 cm⁻¹. Thus, the scaling factor at the M06-2X/6-311++G(2d,2p) level of theory is 0.948 (3472/3661 = 0.948).

^bExperimental Gly_{NH} and $NHBn_{NH}$ frequencies of conformer A of Boc-Gly-^DPro-NHBn-OMe are 3322 and 3437 cm⁻¹, respectively, experimental Gly_{NH} and $NHBn_{NH}$ frequencies of conformer B are 3313 and 3450 cm⁻¹, respectively and experimental Gly_{NH} and $NHBn_{NH}$ frequencies of conformer B are 3324 and 3446 cm⁻¹, respectively. The bold-faced ones in the table are the observed conformers.

4.2.3.3. Pro-Gly IR NH spectra and comparison to experiment

3349 3355	337	07 1 3	3472 3471 3472 ,	$\Delta G_{rel} = 1.64 \text{ kJ/mc}$ $\Delta G_{rel} = 2.17 \text{ kJ/mc}$ $\Delta G_{rel} = 2.19 \text{ kJ/mc}$ $\Delta G_{rel} = 2.88 \text{ kJ/m}$ $\Delta G_{rel} = 3.01 \text{ kJ/mc}$
	34	07 1 3	3471	$\Delta G_{\rm rel}$ = 2.19 kJ/m $\Delta G_{\rm rel}$ = 2.88 kJ/m
	3378	3	3471	∆G _{rel} = 2.88 kJ/m
33	-			
33	34	04,	3472.	$AG_{1} = 3.01 k l/m$
33				
	59	3395		∆G _{rel} = 3.31 kJ/m
3	360	3396		$\Delta G_{\rm rel}$ = 3.98 kJ/m
33	356	3397		$\Delta G_{\rm rel}$ = 4.09 kJ/m
3343		3398		∆ G _{rel} = 4.40 kJ/m
	3393		3444	∆G _{rel} = 4.48 kJ/m
	3367		3479	∆G _{rel} = 4.55 kJ/m
	3367		3478	∆G _{rel} = 4.96 kJ/m
		3403	3471	∆G _{rel} = 5.36 kJm
	3369		3478	∆G _{rei} = 6.13 kJ/m
		3410	3472	∆G _{rel} = 6.56 kJ/m
-	33	3356 3343 3393 3367 3367 3369	3356 3397 3343 3398 3393 3367 3367 3403 3369 3410	3356 3397 3343 3398 3393 3444 3367 3479 3367 3478 3403 3471 3369 3478 3410 3472

Figure S25. Comparison of the experimental IR spectra with the theoretical IR spectra of the twelve low energy conformers of Boc-^DPro-Gly-NHBn-OMe calculated at the M06-2X/6-311++G(2d,2p) level of theory. Scaling has been done by taking Z-Gly-OH molecule as reference. Scaling factor is 0.948 at this particular level of theory. The theoretical stick spectra, which are color coded, are the predicted structures for the observed conformers in the experiment.

Conf. A	3346	3391			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	
Com. D	3365	3363 34	PG1-C	7 _D -C7 _L -g [†] - C	∆G _{rel} = 0.00 kJ/	mol
	3308	3369	PG10-0	C7 _D -C7 _L -g⁻- t	∆G _{rel} = 1.30 kJ/	mol
	3308	3369	PG3-C	7 _D -C7 _L -g [⁺] - t	∆G _{rel} = 1.31 kJ/	mol
	3309	3368	PG2-C	7 _D -C7 _L -g [⁺] - t	∆G _{rel} = 2.70 kJ/	mol
PG11-C7 _D -C7 _L -g ⁺ -	t	3395	3435		∆G _{rei} = 4.12 kJ	/mol
PG6-F-C10-g⁻- t		3392		3483	∆G _{rel} = 7.77 kJ	/mol
PG7-C7 _D -C7 _L -g⁻- C	3324	33	386		∆G _{rel} = 7.79 kJ	l/mol
PG4-F-C10-g⁻- C		3	390	3483	∆ G _{rel} = 8.42 kJ	/mol
PG5-F-C10-g⁻- C		3357		3475	∆G _{rel} = 9.33 kJ	l/mol
PG8-C7 _D -C7 _L -g⁻- t	3324	3	387		∆G _{rel} = 9.64 kJ	/mol
PG9-C7 _D -C7 _L -g⁻- t	3324	3	387		∆G _{rel} = 9.66 kJ	/mol
PG13-F-C10-t-c		3355		3479	∆G _{rel} = 9.69 kJ	/mol
PG12-F-C10-t-c		3355		3480	∆G _{rel} = 9.76 kJ	/mol
PG14-F-C10-g [⁺] - t			3396	3479	∆G _{rel} = 9.76 kJ	l/mol
PG16-F-C10-g [⁺] - C			3400	3479	∆G _{rei} = 11.04 kJ	l/mol
PG15-F-C7 _L -g ⁺ - c		3355		3482	∆G _{rel} = 11.18 kJ	l/mol
50 3300	335	The second second second	400 nber (cm ⁻¹)	3450	3500	35

Figure S26. Comparison of the experimental IR spectra with the theoretical IR spectra of the twelve low energy conformers of Boc-^DPro-Gly-NHBn-OMe calculated at the B3LYP-D3/def2TZVPP level of theory. Scaling has been done by taking Z-Gly-OH molecule as reference. Scaling factor is 0.958 at this particular level of theory.

Conf. A	3346		3391			~~~~~~	•
	3365		V	3411			
3289		3359		PG1-C7	_D -C7 _L -g [⁺] - C	∆G _{rel} = 0.00	kJ/mol
3292	-	3363		PG3-C7	_D -C7 _L -g [⁺] - t	∆ G _{rel} = 2.99	€ kJ/mol
3292		3363		PG10-C	7 _D -C7 _L -g⁻- t	∆ G _{rel} = 2.99	kJ/mol
3294		3361		PG2-C7	_D -C7 _L -g [⁺] - t	∆G _{rel} = 4.32	2 kJ/mol
PG11-C7 _D -C7 _L -g [⁺] - t		3383	3	3409		∆ G _{rel} = 6.22	2 kJ/mol
33	311	3391		PG9-0	C7 _D -C7 _L -g⁻- t	$\Delta G_{\rm rel}$ = 6.5	8 kJ/mol
PG6-F-C10-g⁻- t		3395			3475	∆ G _{rel} = 6.88	8 kJ/mol
PG4-F-C10-g⁻- c			3389		3473	∆ G _{rel} = 7.7	6 kJ/mol
PG7-C7 _D -C7 _L -g⁻- c	3315		3392			∆ G _{rel} = 8.45	5 kJ/mol
PG14-F-C10-g [⁺] - t			3397	8	3469	∆ G _{rel} = 8.53	8 kJ/mol
PG15-F-C7 _L -g [⁺] - c		3354			3473	∆ G _{rel} = 8.59) kJ/mol
PG16-F-C7 _∟ -g [⁺] - C	3	354			3473	∆ G _{rel} = 8.59) kJ/mol
PG5-F-C10-g⁻- c		3356			3470	∆ G _{rel} = 9.59	9 kJ/mol
PG8-C7 _D -C7 _L -g⁻- t	3318	34	02			∆ G _{rel} = 9.83	7 kJ/mol
PG13-F-C10-t-c	3	351			3475	∆ G _{rel} = 11.3	3 kJ/mol
PG12-F-C10-t-c	_3	353			3475	∆G _{rei} = 11.6	8 kJ/mol
50 3300	3350	Wavenu	3400 umber (4	3450	3500	35

Figure S27. Comparison of the experimental IR spectra with the theoretical IR spectra of the twelve low energy conformers of Boc-^DPro-Gly-NHBn-OMe calculated at the B97-D3/def2TZVPP level of theory. Scaling has been done by taking Z-Gly-OH molecule as reference. Scaling factor is 0.975 at this particular level of theory.

Conf. A	3346	3391	~~~~~~	~~~~~
PG10-C7 _D -C7 _L -g⁻- t	3365	√34 ⁴ 3365	11	∆G _{rel} = 0.00 kJ/mol
13	3310	3368 PG1	-C7 _D -C7 _L -g ⁺ - c	$\Delta G_{\rm rel}$ = 0.80 kJ/mol
PG6-F-C10-g⁻- t		3392	3478	∆G _{rel} = 4.99 kJ/mol
PG5-F-C10-g⁻- c	335	53	3479	∆G _{rel} = 5.27 kJ/mol
	3315 337	7 PG2-C	7 _D -C7 _L -g [⁺] - t	∆G _{rel} = 6.36 kJ/mol
PG4-F-C10-g⁻- c		3396	3485	$\Delta G_{rel} = 7.38 \text{ kJ/mol}$
PG11-C7 _D -C7 _L -g [⁺] - t		3387	3438	∆G _{rel} = 7.68 kJ/mol
	3320	3359 PG3-C7 _D -	C7 _L -g [⁺] - t	∆G _{rel} = 7.74 kJ/mol
PG12-F-C10-t-c		3365	3483	∆G _{rel} = 9.44 kJ/mol
PG13-F-C10-t-c	33	55	3483	$\Delta G_{rel} = 9.79 \text{ kJ/mol}$
PG15-F-C7 _L -g [⁺] - c	33	357	3483	∆G _{rel} = 10.11 kJ/mo
PG16-F-C7 _L -g ⁺ - c	3	357	3483	∆G _{rel} = 10.11 kJ/mo
PG7-C7 _D -C7 _L -g⁻- C	3334	3385		∆G _{rel} = 10.24 kJ/mol
PG14-F-C10-g [⁺] - t		3398	3481	∆ <i>G</i> _{rel} = 10.88 kJ/mo
PG8-C7 _D -C7 _L -g⁻- t	3330	3387		$\Delta G_{\rm rel} = 17.51 \text{ kJ/mol}$
PG9-C7 _D -C7 _L -g⁻- t	3330	3387		∆G _{rel} = 17.57 kJ/mol
50 3300	3350 Wa	3400 Ivenumber (cm ⁻¹	3450	3500 3

Figure S28. Comparison of the experimental IR spectra with the theoretical IR spectra of the twelve low energy conformers of Boc-^DPro-Gly-NHBn-OMe calculated at the ω B97X-D/def2TZVPP level of theory. Scaling has been done by taking Z-Gly-OH molecule as reference. Scaling factor is 0.945 at this particular level of theory.

4.2.3.4. Pro-Gly unscaled and scaled NH frequencies for M06-2X/6-311++G(2d,2p)

Table S2. Harmonic and scaled NH stretching frequencies of all the 16 low energy conformers of Boc-^DPro-Gly-NHBn-OMe peptide calculated at the M06-2X/6-311++G(2d,2p) level of theory.^a

	Glycine _N	$_{\rm HH}({\rm cm}^{-1})$	NHBn	_{NH} (cm ⁻¹)
Conformers	Harmonic v _{N-H}	Scaled v_{N-H}	Harmonic v _{N-H}	Scaled v_{N-H}
PG1-C7 _D -C7 _D -g ⁺ -c	3524	3340	3567	3381
PG2-C7 _D -C7 _L -g ⁺ -t	3533	3349	3582	3395
$PG3-C7_D-C7_L-g^+-t$	3538	3355	3560	3375
PG4-F-C10-g ⁻ -c	3663	3472	3593	3407
PG5-F-C10-g ⁻ -c	3662	3471	3564	3378
PG6-F-C10-g ⁻ -t	3663	3472	3591	3404
РG7-C7 _D -C7 _L -g ⁻ -с	3543	3359	3581	3395
PG8-C7 _D -C7 _L -g ⁻ -t	3545	3360	3582	3396
PG9-C7 _D -C7 _L -g ⁻ -t	3540	3356	3583	3397
PG10-C7 _D -C7 _L -g ⁻ -t	3526	3343	3584	3398
$PG11-C7_{D}-C7_{L}-g^{+}-t$	3633	3393	3579	3444
PG12-F-C10-t-c	3670	3479	3552	3367
PG13-F-C10-t-c	3669	3478	3552	3367
PG14-F-C10-g ⁺ -t	3662	3471	3590	3403
PG15-F-C7 _L -g ⁺ -c	3669	3478	3554	3369
PG16-F-C10-g ⁺ -c	3662	3472	3597	3410

^aThe same scaling factor 0.948, which has been used for the Boc-Gly-^DPro-NHBn-OMe peptide at the M06-2X/6-311++G(2d,2p) level of theory, has been used for the Boc-^DPro-Gly-NHBn-OMe peptide at the same level of theory. Experimental Gly_{NH} and NHBn_{NH} frequencies of conformer A of Boc-^DPro-Gly-NHBn-OMe are 3346 and 3391 cm⁻¹, respectively, while experimental Gly_{NH} and NHBn_{NH} frequencies of conformer B are 3365 and 3411 cm⁻¹, respectively. The bold-faced ones in the table are the observed conformers.

4.3. Energy-ordered conformers obtained using solvent calculations

Table S3. A comparison between PCM (chloroform) and gas-phase DFT calculations at the B3LYP- D3/def2-TZVPP level of theory for low-energy conformers of Gly-Pro sequence. The nomenclature is the same as that followed for the gas phase, namely based on the ordering and conformer type observed in M06-2X/6-311++G(2d,2p) in the gas phase. The relative energetics of the conformers change upon solvation, but the nature of the conformers does not change. Hence in both gas and condensed phases, C5-C7_D conformers are favorably formed compared to the C10 orientation.

Conformers	$\Delta G_{\rm rel}$ at 300	K (kJ/mol)
Comorniers	РСМ	Gas-Phase
GP6-C5-C7 _D -g ⁺ -c	0.00	5.77
$GP7-C5-C7_{\mathrm{D}}-g^{+}-t$	0.02	1.35
GP5-C5-C7 _D -g ⁻ -t	0.02	1.36
GP4-C5-C7 _D -g ⁻ -c	0.27	0.01
$GP8-C5-C7_{\mathrm{D}}-g^{+}-t$	0.53	5.81
GP2-C5-C7 _D -g ⁻ -t	0.79	1.36
GP3-C5-C7 _D -g ⁻ -t	0.79	0.00
GP1-C5-C7 _D -g ⁻ -c	0.81	5.95
GP10 C5-C7 _D -g ⁻ -c	0.93	6.56
GP12-F-C7 _D -g ⁻ -t	2.12	6.53
$GP9-C5-C7_{D}-g^{+}-c$	5.23	6.08
GP11-F-C10-g ⁺ -t	6.06	6.74
GP13-F-C10-g ⁺ -t	6.06	9.88

Table S4. A comparison between PCM and gas-phase DFT calculations at the B3LYP-D3/def2TZVPP level of theory for low-energy Pro-Gly system. Here we find that the C10 conformers are stabilized more than the C7-C7 conformers; this is in agreement with experimental findings in chloroform solvent. Here also we found that the C10 conformers in the gas phase stabilized in the solvent phase, none of the conformers interconverted into the other due to solvation.

	$\Delta G_{\rm rel}$ at 300 K (kJ/mol)	
Conformers	PCM (chloroform)	Gas-Phase
PG6-F-C10-g ⁻ -t	0.00	7.77
PG4-F-C10- g ⁻ -c	1.94	8.42
$PG1-C7_D-C7_L-g^+-c$	2.89	0.00
PG13-F-C10-t-c	3.85	9.69
PG13-F-C10-t-c	4.42	9.76
$PG3-C7_D-C7_L-g^+-t$	5.00	1.31
PG10-C7 _D -C7 _L -g ⁻ -t	5.01	1.30
PG14-F-C10- g ⁺ -t	5.01	9.76
PG5-F-C10- g ⁻ -c	6.36	9.33
$PG2-C7_D-C7_L-g^+-t$	6.38	2.70
PG16-F-C10- g ⁺ -c	6.47	11.04
PG15-F-C7 _L -g ⁺ -c	7.18	11.18
$PG11-C7_D-C7_L-g^+-t$	8.03	4.12
PG7-C7 _D -C7 _L -g ⁻ -c	12.31	7.79
PG8-C7 _D -C7 _L -g ⁻ -t	12.84	9.64
PG9-C7 _D -C7 _L -g ⁻ -t	12.84	9.66

5. Statistics of the number of the CSD structures containing Gly-Pro and Pro-Gly sequences

A statistics of various non-covalent interactions (C5, C7, and C10) present in the Gly-Pro and Pro-Gly containing peptides was obtained using CCDC conquest 2020 2.0 software. The Cambridge structural database contains numerous structures of organic and inorganic materials.



Figure S29. Statistics of the number of CSD structures having different non-covalent interactions in (a) Gly-Pro and (b) Pro-Gly containing peptides.

6. X-ray single crystal structure

A good quality crystal was obtained for the Boc-Gly-^DPro-NHBn-OMe peptide while the quality of the crystal obtained for the Boc-^DPro-Gly-NHBn-OMe peptide was not suitable for the X-ray diffraction. The crystal of Boc-Gly-^DPro-NHBn-OMe was grown in mixed solvent of ethyl acetate and n-hexane. The crystals were grown through slow evaporation of ethyl acetate and n-hexane solvent mixture. X-ray diffraction of the crystal of Boc-Gly-^DPro-NHBn-OMe was performed using APEX(II) DUO CCD diffractometer. The X-ray data were collected at 100 K temperature. The crystal structure of Boc-Gly-^DPro-NHBn-OMe has been provided in Figure 8 in the manuscript while the details of the structure refinement and crystallographic data are provided in Table S6.

The details of the Ramachandran angles and hydrogen bond parameters of the crystal structure of the Boc-Gly-^DPro-NHBn-OMe peptide have been listed in Table 1 provided in the main text. The crystal structure of Boc-Gly-^DPro-NHBn-OMe shows extended PP-II type structure with C5 intramolecular hydrogen bond with the Gly residue which is qualitatively similar to that observed in the gas phase. However, the C7 hydrogen bond interaction in the crystal structure is negligible as the corresponding N-H...O distance (376 pm) is quite large compared to the acceptable hydrogen bond distance. The deviation of the C7 hydrogen bond in the crystal structure could be due to the crystal packing forces through the intermolecular interaction between the neighbouring units.

Table S5. The details of the crystal structure refinement and crystallographic data for Boc-Gly

 ^DPro-NHBn-OMe

6606	245775	
CCDC	2157775	
Empirical formula	$C_{20}H_{29}N_3O_5$	
M _r	391.46	
Crystal size, mm ³	0.12x0.16x0.20	
Crystal system	Monoclinic	
Space group	P 21	
a, Å	11.7946(9)	
b, Å	9.3562(8)	
c, Å	18.9259(16)	
α, °	90	
β, °	105.551(2)	
γ, °	90	
Cell volume, Å ³	2012.1(3)	
Z ; Z'	4	
Т, К	100	
Radiation type;	ΜοΚα, 0.71073	
wavelength Å		
F ₀₀₀	840	
μ, mm ⁻¹	0.093	
θ range, °	2.234 - 30.170	
Reflections collected	11923	
Reflections unique	5555	
R _{int}	8.35	
Parameters	514	
wR ₂ (all data)	0.1413	

The crystal structure was obtained by direct methods using SHELXS-97.6

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