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Department of Chemistry - Organic Chemistry – C317

Indian Institute of Science Education and Research-Pune

Antiparallel β-Double Helices from α,γ-Hybrid Peptides

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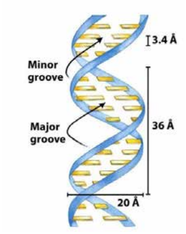
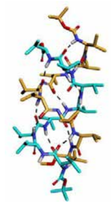
Introduction

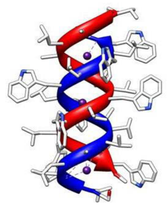
- **Heterooligomers of $(\alpha\beta)_n$-sequences have demonstrated the adoption of 11-, 14/15- and 11/9 helices.**
- **$(\alpha\gamma)_n$-sequences have exhibited the ability to form 12- and 12/10- helical structures.**
- **In contrast to the prevalent protein secondary structures such as α-helix and β-sheets, β-double helices are rare in proteins.**



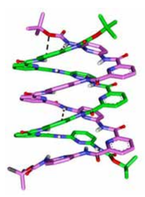
DNA duplex



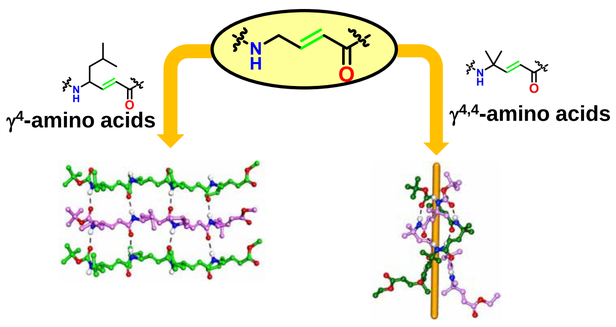
Benedetti *et al.*
Nature **1979**, *282*, 630



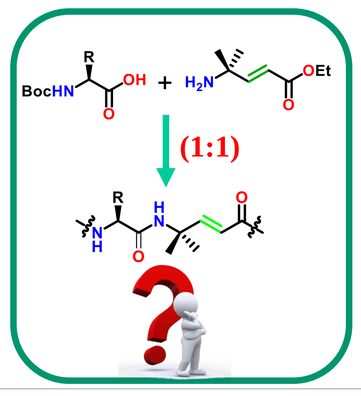
Gramicidin A



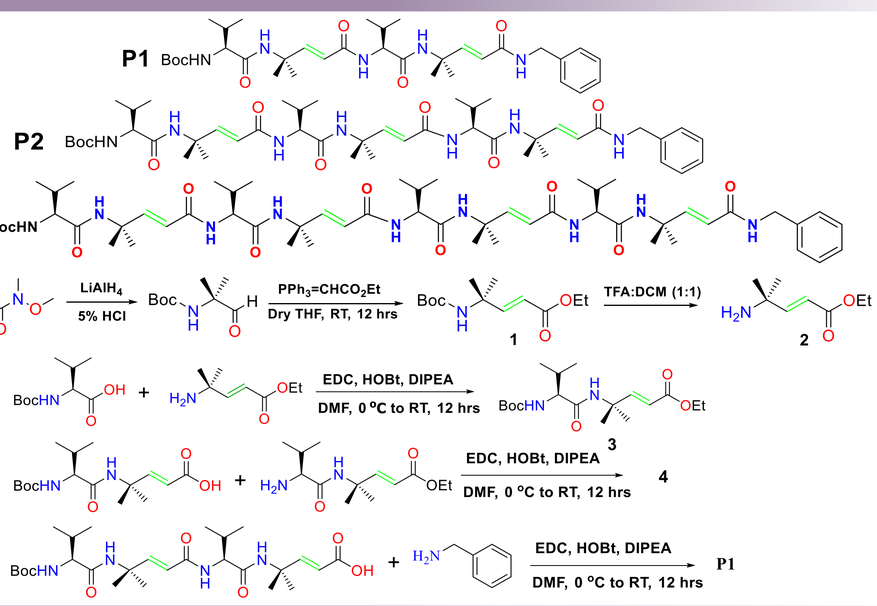
Lehn *et al.*
Nature **2000**, *407*, 720



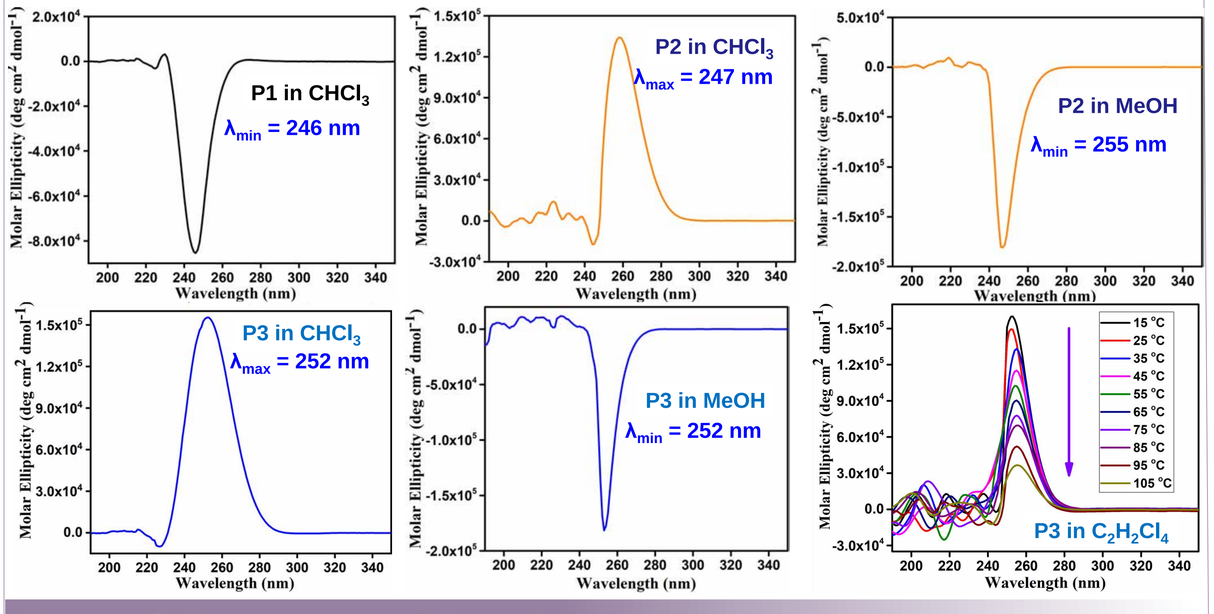
Org. Biomol. Chem., **2019**,17, 9226 *Angew. Chem. Int. Ed*. **2018,** *57*, 1057



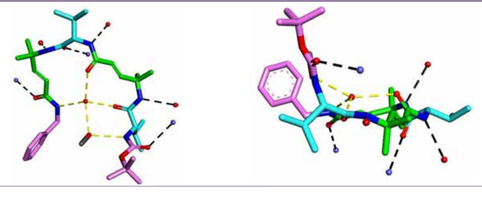
Synthesis Scheme



CD Study of the Peptides P1-P3



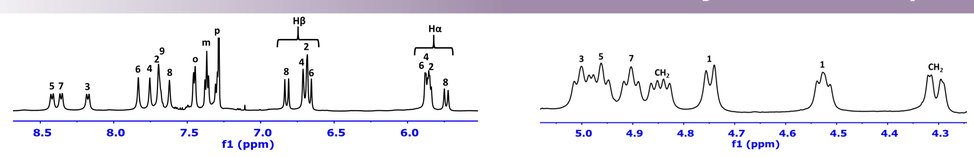
Crystal Structure of Peptide P1



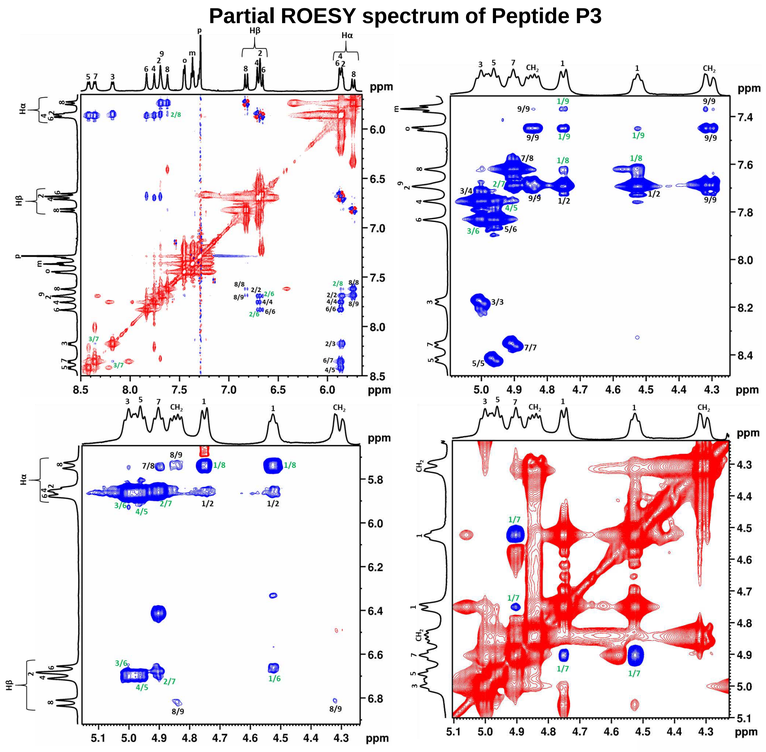
Torsion Angles of P1

Peptide Unit	ϕ	θ1	θ2	Ψ
Val (1)	-88.60	-	-	-127.54
dγAic (2)	45.68	-155.21	-178.24	171.65
Val (3)	-71.92	-	-	143.78
dγAic (4)	81.56	-0.04	177.46	-179.95

Structural Analysis of Peptide P3

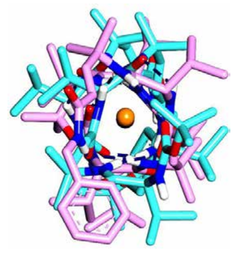


Partial ROESY spectrum of Peptide P3

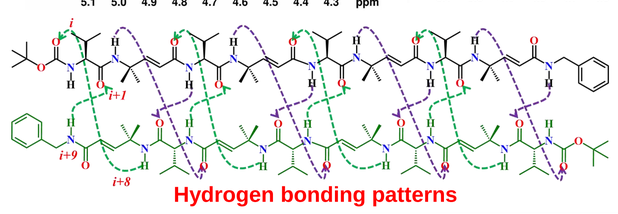


Inter-molecular NOEs – Green
Intra-molecular NOEs – Black

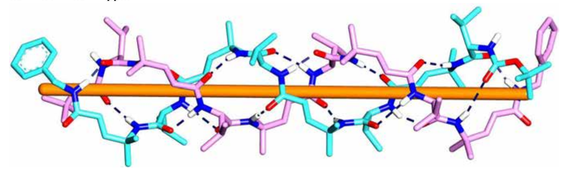
Inter-NOEs	Type
Boc/Pro-S CH_3 (0/7)	Strong
Boc/Pro-R CH_3 (0/7)	Medium
Pro-R CH_3/*Pro-S* CH_3 (3/8)	Medium
Pro-S CH_3/*Pro-R* CH_3 (4/7)	Medium
Pro-R CH_3/*Pro-S* CH_3 (5/6)	Medium
Hβ/NH (2/6)	Weak
Hα/NH (2/8)	Weak
NH/NH (3/7)	Weak
Hβ/NH (6/2)	Weak
NH/Hα (1/7)	Weak
Hα/Hα (1/7)	Very Strong



Top View



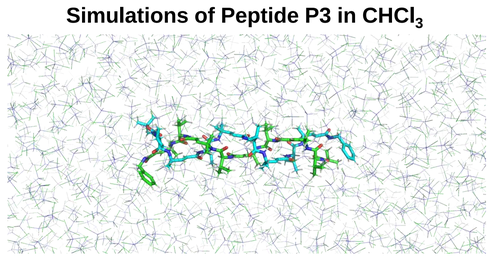
Hydrogen bonding patterns



Anti-Parallel β-Double Helix

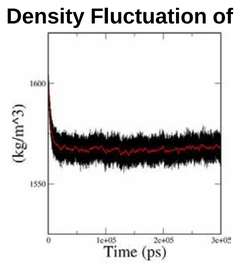
Computational Studies of Peptide P3 in $CHCl_3$

Simulations of Peptide P3 in $CHCl_3$

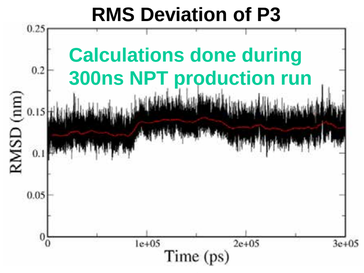


P3 solvated with 9019 molecules of $CHCl_3$ & their stability upto 300 ns

Density Fluctuation of P3

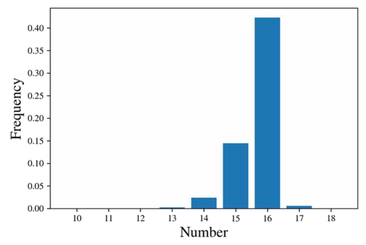


RMS Deviation of P3

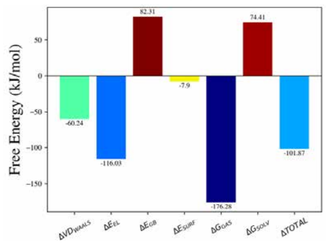


Red line shows the running average of the density & RMS deviation for 1 ns.

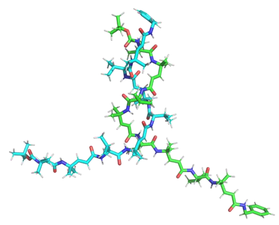
Number of inter strand H-bonds



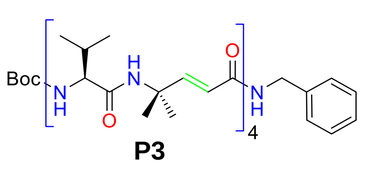
MM-GBSA free energy (101.87 kJ/mol)

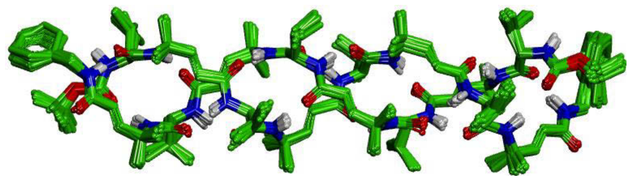


Unbinding Mechanism



Conclusion





- **This is the first example demonstrating that α,γ-hybrid peptides can adopt into anti-parallel β-double helical structures.**
- **Both NMR structural analysis and computational studies revealed the anti-parallel orientation of α,γ-hybrid peptides strand of β-double helix.**
- **The anti-parallel β-double helical structure is stabilized through 16-inter strand H-bonds and its total free energy is around -101.87 kJ/mol.**

Reference

1) Misra, R.; Dey, S.; Reja, R. M.; Gopi, H. N. Artificial β-Double Helices from Achiral γ-Peptides. *Angew. Chemie - Int. Ed.* **2018**, *57*, 1057–1061.
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