Development of Cyclopropane-Based Foldamers Mimicking Protein Secondary Structures

https://doi.org/10.17952/37EPS.2024.P2250

Makoto Nagata, Nanase Ochiai, Akiko Yoshida, Satoshi Shuto, Mizuki Watanabe

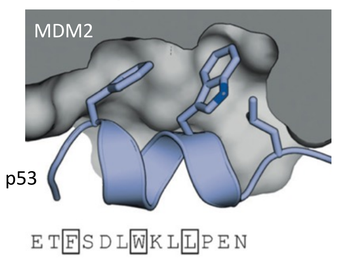
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Hokkaido 060–0812, Japan

E-mail (M.W.)
mwatanab@pharm.hokudai.ac.jp

α-Helix & β-Strand : protein secondary structures

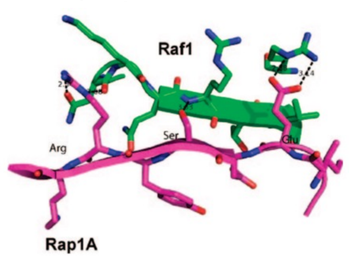
✓ forming hot spots of protein–protein interactions (PPI).

MDM2/p53 interaction



Grossmann, T. N. *et al*. *ACIE* **2015**, *54*, 8896.

Raf1/Rap1 interaction

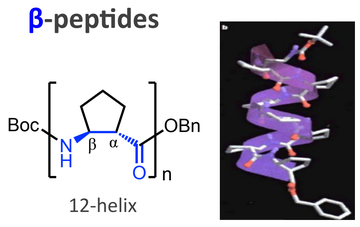


Hamilton, D. *et al. JACS* **2009**, *131*, 4566.

Foldamers : synthetic oligomers forming a specific secondary structure

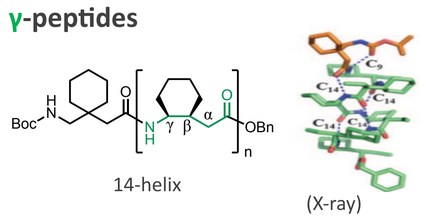
✓ It can mimic the 3D structures and functions of natural α-peptides in proteins.
✓ It can be one of the candidates for PPI inhibitors.
✓ A great many helical peptide-based foldamers have been reported.

β-peptides



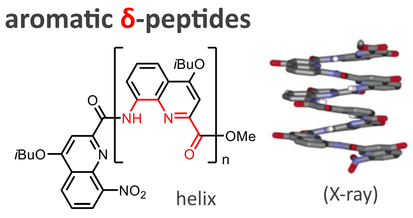
Gellman, S. H. *et al. Nature* **1997**, *387,* 381.

γ-peptides



Gellman, S. H. *et al. ACIE* **2016**, *55*, 11096.

aromatic δ-peptides



Huc, I. *et al. JACS* **2003**, *125,* 3448.

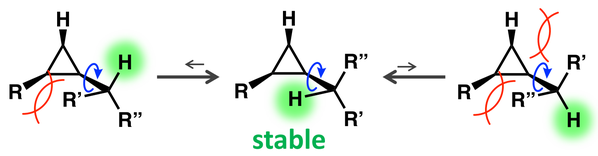
On the other hand, there are **few reports on aliphatic δ-peptide & β-strand-like foldamers.**

Structural properties of cyclopropane

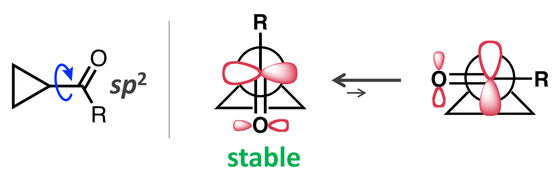
Cyclopropane can control the molecular conformation.

✓ *Trans/cis* restriction

✓ Cyclopropylic strain

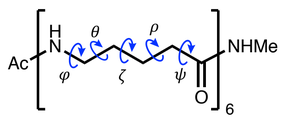


✓ Bisected conformation preference

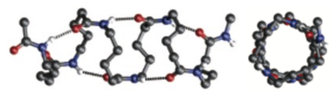


Shuto, S. *et al. Chem. Eur. J.* **2017**, *23*, 14394.

Design of helical δ-peptide foldamer



When adapting a 14-helix...

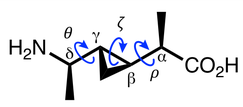


(HF/6-31G* ab initio MO theory)

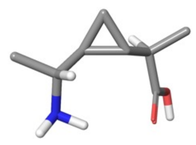
compounds	Torsion angles (°) φ	θ	ζ	ρ	ψ
14-helical unsubstituted linear δ-hexapeptide	106.5	–72.8	171.6	–76.9	113.7

Hofmann, H.-J. *et al. J. Org. Chem*. **2004**, *69*, 6214.

δ-Disubstituted cyclopropane δ-amino acid (Cp-δ-aa)

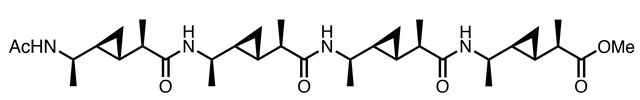


—	–86.0	139.7	–89.0	—
	gauche⁻	*trans*	*gauche*⁻	

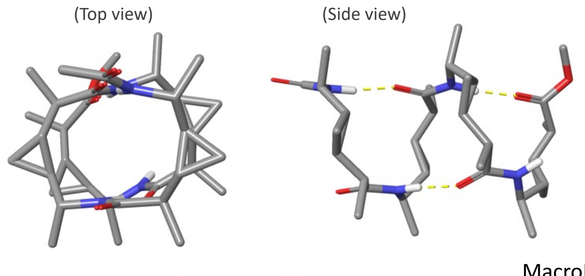


MacroModel 10.9, MMFFs; H_2O

Oligomer of Cp-δ-aa



(Top view) (Side view)



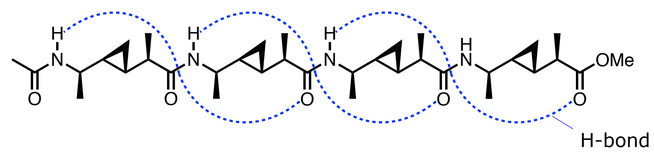
Predicted 3D structure

MacroModel 10.9
MMFF94s; H_2O

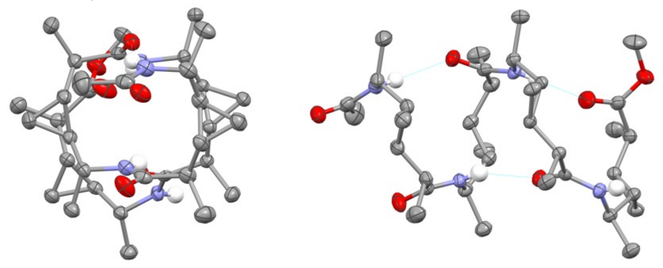
right-handed 14-helical structure

Structural analysis of Cp-δ-peptides

by X-ray diffraction of crystal

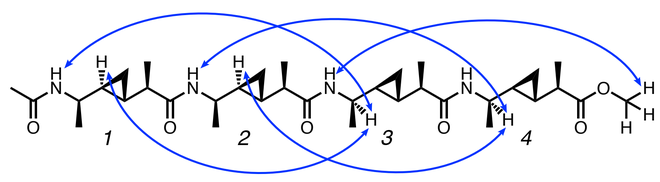


(Top view) (Side view)



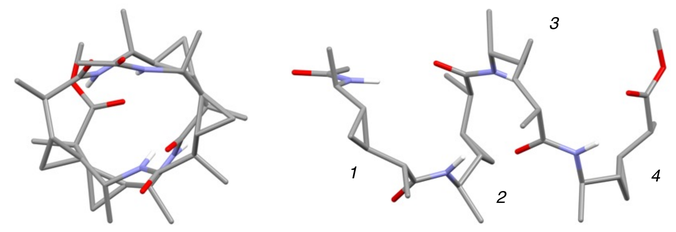
by 2D NMR spectra (CD$_3$OH, 600 MHz)

: Observed NOE correlations



The lowest-energy 3D structure from the NMR-based calculations

(Top view) (Side view)

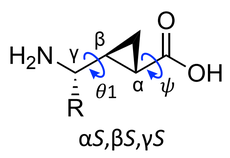


The Cp-δ-peptides were the 14-helices, as expected by the molecular design, in solution and crystal.

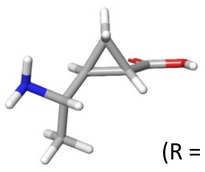
Watanabe, M.; Shuto, S. *et al. Org. Biomol. Chem.* **2023**, *21*, 970.

Design of β-strand-like foldamer

γ-Substituted cyclopropane γ-amino acid (Cp-γ-aa)

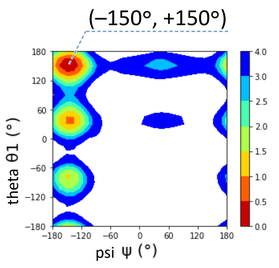


αS,βS,γS



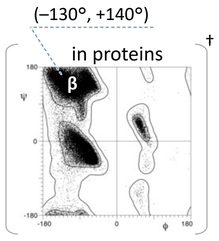
(R = Me)

Predicted stable conformation



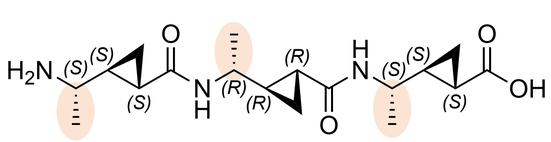
Ramachandran plot

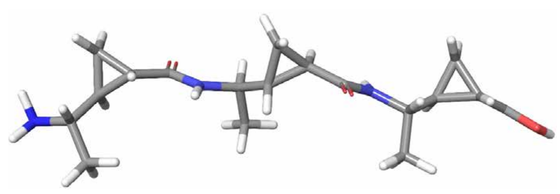
DFT : B3LYP/6-31+G*



†Lovell, S. C. *et al. Proteins* **2003**, *50*, 437.

Oligomer : Alternate coupling of a pair of enantiomers of Cp-γ-aa





Predicted 3D structure

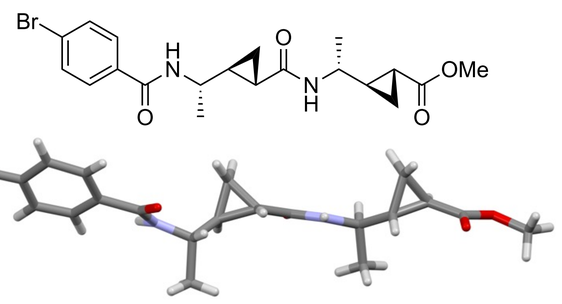
MacroModel 10.9
MMFF94s; H_2O

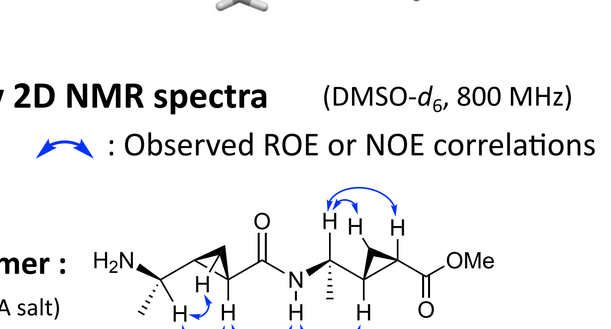
β-strand-like structure

with the oriented side chain to the same face, corresponding to the *i*, *i*+2, *i*+4 residues of β-strand

Structural analysis of Cp-γ-peptides

by Micro ED method



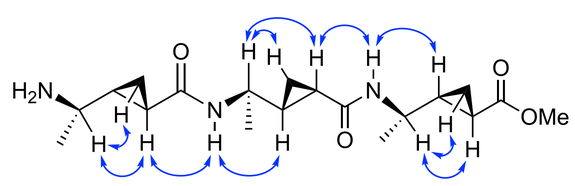


by 2D NMR spectra (DMSO-d_6, 800 MHz)

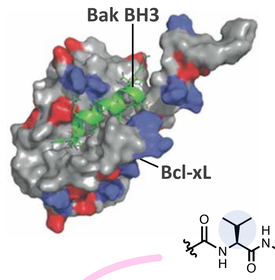
: Observed ROE or NOE correlations

2-mer : (TFA salt)

3-mer : (HCl salt)

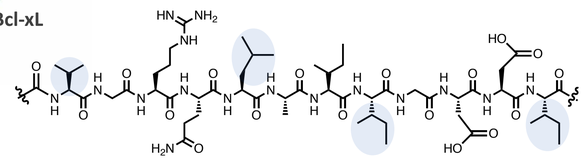


α/Cp-δ-mixed peptides as PPI inhibitors

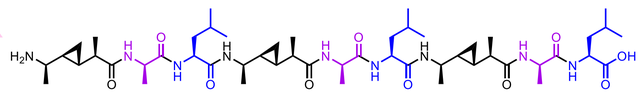


Bak BH3 domain

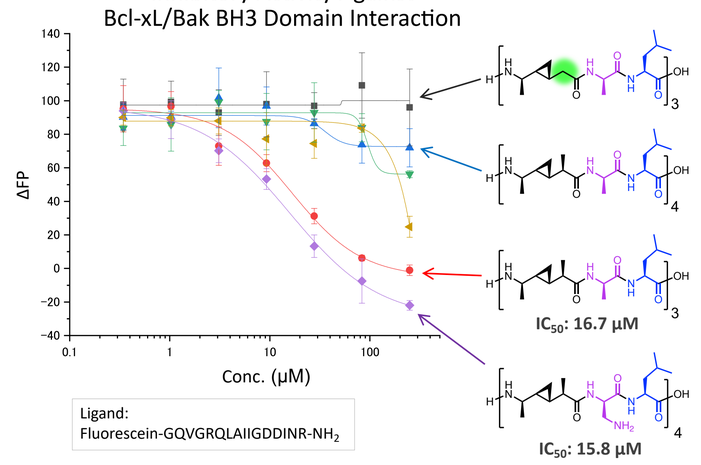
Hot spot V G R Q L A I I G D D I
i *i*+4 *i*+7 *i*+11



Mimicking



Inhibitory Activity Against Bcl-xL/Bak BH3 Domain Interaction



Ligand:
Fluorescein-GQVGRQLAIIGDDINR-NH_2

Acknowledgements

Special thanks to Prof. Koh Takeuchi (The Univ. of Tokyo) & Dr. Hiroyuki Kumeta (Hokkaido Univ.) for their help in conducting the NMR measurements

Special thanks to Ms. Marin Yokomine & Assoc. Prof. Jumpei Morimoto (The Univ. of Tokyo) for their help in conducting the inhibitory activity assay