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量子化学計算を用いたαフッ素化ジペプチドの立体配座に関する解析

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Analysis of the Conformations of α-Fluorinated Dipeptide using Quantum Chemical Calculations ([1]*Faculty of Engineering, Kyoto University,* [2]*Graduate School of Engineering, Kyoto University,* [3]*University of the Ryukyus, Research Facility Center,* [4]*Graduate School of Science, University of Hyogo,* [5]*Graduate School of Engineering and Science, University of the Ryukyus,* [6]*Faculty of Science, University of the Ryukyus,* [7]*Fukui Institute for Fundamental Chemistry, Kyoto University,* [8]*Graduate School of Informatics, Nagoya University*) ○Hikaru Oshimo[1], Kanami Sugiyama[2], Genta Kojya[3], Tomohiro Agou[4], Hisanori Arakaki[5], Riko Genka[5], Satoru Arimitsu[6], Hirofumi Sato[2,7], Masahiro Higashi[8]

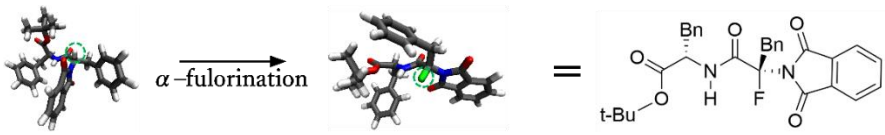
The fluorine substitution is known to have a significant effect not only on a molecule's physiological and electronic properties but also on its stereochemical conformations, attracting significant attention as a strategy for controlling stereochemistry. An α-fluorinated dipeptide synthesized recently by our experimental group also showed a conformation different from the corresponding non-fluorinated dipeptide (the figure below).

In this study, the conformational differences between fluorinated and non-fluorinated dipeptides were investigated by DFT calculations and the natural bond orbital (NBO) analysis. We found specific interactions on the most stable conformation of the fluorinated, where several dihedral angles involving the fluorine substituent exhibited high rotational barriers. Notably, stereoelectronic effects, such as the anomeric effect arising from hyperconjugation for the antibonding C–F σ* orbital as an acceptor, and hydrogen bonding between fluorine and hydrogen, were found to play a crucial role in determining the stable conformation.

Keywords : Dipeptide, Fluorination, Conformation, Density Functional Theory

フッ素置換基の導入は、分子への生理的・電子的な機能の付与に加えて、立体配座に対しても大きな影響を及ぼすことが知られており、立体化学を制御する方法の一つとして注目されている[1)]。近年、我々の実験グループで合成に成功したαフッ素化ジペプチドの立体配座も未置換体とは大きく異なることが明らかになった（下図）。

本研究では、DFT 計算及び自然結合軌道（NBO）法を用いてフッ素化体と未置換体の立体配座の違いを解析した。その結果、フッ素化体の最安定配座には特異的な相互作用が働いており、フッ素置換基を一端とする複数の二面角は高い回転障壁を有した。具体的には、反結合性 C–F σ*軌道をアクセプター準位とした超共役に起因するアノマー効果等の立体電子効果や、F–H 間の水素結合が安定配座の決定に重要な役割を果たすことを見出した。



1) C. Thiehoff, Y. P. Rey, R. Gilmour, *Isr. J. Chem.,* **2017**, 57, 92.