Cooperative n → π* interactions via thionated peptoid side chains for promoting PPII helix.

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Age-related diseases such as Alzheimer's disease (AD) and cancer have become a pressing global healthcare problem, and implicated in these diseases are defective protein-protein interactions in cellular signaling pathways. Of particular interest to the researchers is a ligand-binding site known as the WW domain, which has been shown to be integral to the protein interactions of AD and cancer. This domain preferentially and promiscuously binds the polyproline type II helix. Therefore, by designing biological probes that can form PPII helices that can bind to the WW domain, one would be able to understand the structure and function of the domain. Peptoids, or *N*-substituted glycine oligomers, were chosen due to their desirable traits such as biostability and predictable secondary structures; however, amide isomerism arising from the lack of steric repulsion in the backbone hinders designing peptoids that adopt a single conformation. It has been shown that PPII helices only form when the peptoid backbone bonds adopt *trans* conformations, as opposed to *cis* conformation. A promising strategy to regulate the *cis*/*trans* isomerism is to strengthen the $n \rightarrow \pi^*$ interaction (interaction in which a nucleophile donates an electron pair to the empty π^* orbital of a nearby carbonyl group) in the sidechain to backbone directionality. This can be achieved through the thionation of the amides, which involves replacing oxygen of the carbonyl group with sulfur. Interestingly, a previous study involving thionation at one peptoid residue site showed that not only did thionation induce conformational preference towards *trans* backbone amide bond, but it also reversed the conformational preferences at adjacent sites that were not thionated (Conwell, 2018). This led to the conclusion that $n \rightarrow \pi^*$ interactions are cooperative. Therefore, the aim of the project was to synthesize a peptoid that incorporates the thioamide side chain at multiple residue sites to explore the effects of cooperativity on peptoid conformation.

The project first involved the synthesis of the alanine side chain, (*S*)-*2*-amino-*N*,*N*-dimethylpropanamide: Boc-Ala-OH was dissolved in dichloromethane, 2M dimethyl amine in THF, EDCI, and DIPEA and was deprotected using HCl/dioxane. Upon the confirmation of the side chain purity using ^{1}H NMR, a peptoid probe was created using the solid phase synthesis protocol, which involves subjecting F-moc resin to an alternating series of bromination and amination until a peptoid of desired length is reached. This process was monitored using liquid chromatography–mass spectrometry (LC-MS). For the summer, two tetrameric peptoids were synthesized: the first peptoid incorporated *s-1-phenethylamine* at residue site 1 and the alanine side chain at the other three sites, and the second peptoid incorporated the alanine side chain at the other four sites. The future steps will involve the thionation of the peptoids using Lawesson's reagent and the structural analysis of the synthesized peptoids to investigate the effects of cooperativity.

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References

Conwell, S. (2018). *Thionation of Peptoid α-Aminoamide Side Chains for Polyproline Type II Helix Mimicry* [Honors thesis, Bowdoin College]. George J. Mitchell Department of Special Collections & Archives.