Thionation of Peptoid α–Aminoamide Side Chains for Polyproline Type II Helix Mimicry

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A greater understanding of cell signaling pathways is becoming increasingly important as age-related diseases like Alzheimer's Disease increase in prevalence.[1] These pathways can be better understood using biological probes to understand the interactions between proteins in the body. Cell signaling pathways allow for cellular communication within the body. When these communications run awry, it can cause disease.[2,3] A cell signaling domain of particular interest is the WW Domain. This domain is known to act in pathways that have been linked to Alzheimer's Disease and cancer.[4,5] This domain preferentially binds to the polyproline type II (PPII) conformation of proteins.[6] Thus, a molecule that could form and maintain this PPII shape could interact with this domain as proteins do.[7] Polypeptides have the ability to adopt this shape, but they are rapidly broken down in the body by the enzymes that break down proteins because they have the similar primary structure made of amino acids as proteins do. Peptoids, however, are *N*-substituted glycine oligomers, so that the R-group is found on the nitrogen of each monomer, rather than on the carbon as in a peptide. This difference in structure protects peptoids from enzymatic breakdown, and they are, therefore, much more biostable.[8] Peptoids are an exciting class of molecules with a great potential to increase the understanding of how cell signaling pathways work.

The desired PPII helix shape is favored by *trans* amide bonds, while its counterpart, the PPI helix, is favored by *cis* amide bonds.[9] The *cis* and *trans* conformations of a peptoid are in equilibrium with each other, as the molecule can rotate freely around the amide bonds. To maintain and stabilize a PPII helix, therefore, the *trans* conformation must be stabilized, which can be done using $n \rightarrow \pi^*$ interactions, whereby lone pair electrons on a carbonyl oxygen donate into the π^* orbital of a neighboring carbonyl carbon.[10] The presence of exclusively $n \rightarrow \pi^*$ interactions from the side chain to the backbone (rather than from backbone to side chain) has been shown to encourage formation of a PPII helix.[11]

In order to create $n \rightarrow \pi^*$ interactions solely from the side chain to the backbone, the energy of the electrons on the side chain can be increased by thionation. Sulfur is much less electronegative than oxygen, destabilizing lone pair electrons and increasing their affinity for donation to the backbone π^* orbital. Thus, one would hope to thionate only the side chain amide in order to influence the directionality of the $n \rightarrow \pi^*$ interactions.

This year in my Honors Project, I was able to synthesize a peptoid trimer with an oxoamide side chain and then thionate the side chain. I have used solution phase synthesis to build the trimer from three amine or amide monomers and have been able to thionate the amide side chain with Lawesson's reagent. I found that the oxoamide side chain-containing peptoid adopted a *cis* backbone amide bond, likely because it engaged in $n \rightarrow \pi^*$ interactions from the backbone to the side chain, whereas the thioamide side chain-containing peptoid adopted a *trans* backbone amide bond, likely because it engaged in $n \rightarrow \pi^*$ interactions from the side chain to the backbone. Thus, I have been able to modify my molecule to encourage specific interactions, and this knowledge can hopefully be used to make a peptoid with exclusively *trans* backbone amide bonds that forms a polyproline type II helix.

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