Investigation of $n \rightarrow \pi^*$ in peptoids and thiopeptoids

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Many life-threatening diseases are caused by dysregulated protein-protein interactions. Examining inhibitors of these interactions could provide insight into how these diseases progress. Although small peptides could be useful for interrupting these interactions, they are typically not biostable and thus are quickly destroyed by the body’s enzymes. A solution to this problem, however, lies in peptidomimetics — molecules that are structurally similar to peptides but more biostable (Figure 1). Peptoids, a specific kind of peptidomimetic class, could be useful for interrupting protein-protein interactions due to their biostability and propensity to form three-dimensional structures mimicking those of peptides and proteins. However, not much is known about how peptoids fold into such biologically active structures.

My research examined a newly discovered interaction, called an $n \rightarrow \pi^*$ interaction, that is believed to affect peptoid folding. These interactions are thought to occur in peptoids between the lone electron pairs on the carbonyl oxygen and empty $\pi^*$ orbitals of the benzene ring side chain (Figure 2). This interaction is significant because it could play an important role in stabilizing biologically active peptoid structures.

To determine the importance of this interaction, I synthesized model peptoid and thiopeptoid monomers with different benzene ring substituents that were predicted to affect the strength of the $n \rightarrow \pi^*$ interaction (Figure 3). The peptoids and thiopeptoids were synthesized using a previously determined procedure though modifications were made to improve reaction yields. Once synthesized, the propensities of the peptoids or thiopeptoids to adopt the desired structures were determined using NMR spectroscopy.

My research suggested that adding electron withdrawing groups onto the benzene ring strengthens $n \rightarrow \pi^*$ interactions in peptoids. Similarly, replacing the carbonyl oxygen with sulfur also strengthens $n \rightarrow \pi^*$ interactions compared to their peptoid counterparts. This is strong evidence that $n \rightarrow \pi^*$ interactions could potentially have a significant impact on the shapes and structural stabilities of peptoids. This research has led to a better understanding of what influences peptoid folding, which could be used to construct inhibitors of protein-protein interactions that play a role in human disease.

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1B. Gorske; B. Bastian; G. Geske; Blackwell, H., Local and tunable $n \rightarrow \pi^*$ interactions regulate amide isomerism in the peptoid backbone. JACS 2007, 129 (29), 8928-8929.