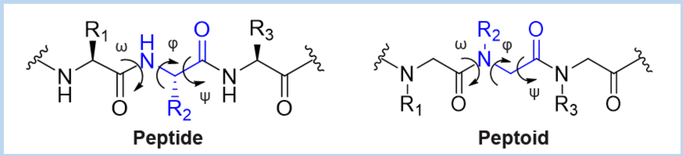
The Synthesis of Hydrogen Bonding Ortho-substituted Benzaldehyde Hydrazone Peptoid Monomers

Brandon Lowe and Daryle Fish

Abstract

Peptides are sequences of amino acids that combine to form proteins, which are essential macromolecules with a wide variety of functions resulting from the structural interactions between chemical groups on the amino acids. This integral structure/function relationship of proteins has left scientists with a desire to synthesize amino acid derivatives with different chemical group substituents. One particular class of peptide derivatives are peptoids, which are *N*-substituted glycine residues.[1]

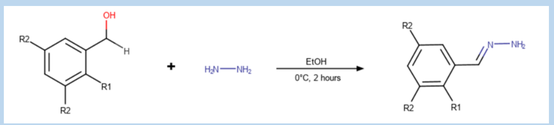
Figure 1: Peptide vs. Peptoid structure with backbone angles labeled



For this research, the goal was to synthesize peptoid monomers which would induce a typically unfavorable *cis*-oriented backbone structure with respect to the ω angle. The substituents chosen were selected based on principles from literature that had showed favorable progress towards the stabilization of the *cis*- backbone structure.

Synthesis Procedures

The general scheme for the initial amination reaction is shown below, and aldehyde substituents are revealed. Yields for all schemes were not calculated as reactions were performed for product identification only.

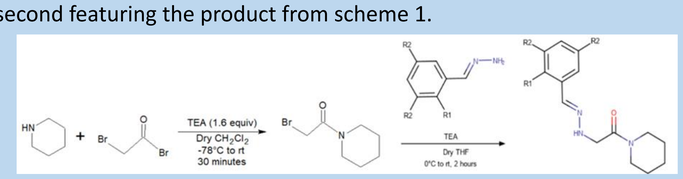


Scheme 1: Aldehyde amination reaction scheme

Aldehyde	R1	R2
Salicylaldehyde	-OH	-H
3,5-dibromosalicylaldehyde	-OH	-Br

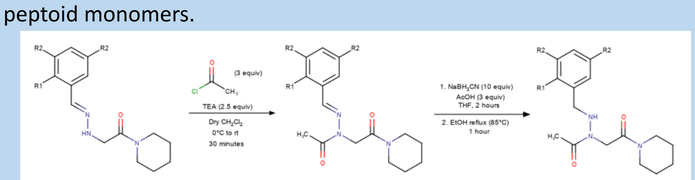
Table 1: Aromatic substituents on chosen aldehydes

The scheme below highlights the two subsequent reactions, with the second featuring the product from scheme 1.



Scheme 2: Initial bromination reaction and subsequent substitution reaction scheme

Had the substitution reaction above proceeded successfully, the reactions in the scheme below should have resulted in completed peptoid monomers.



Scheme 3: Scheme of projected (uncompleted) final reactions using methodology from previous research at NC State University [2]

Experimental Results

Figure 2: Mass spectrum (MS) from the bromination reaction in scheme 2, accompanied by the presumed fragments. This product eluted at 7.62 minutes in the gas chromatograph (GC) as a lone, sharp peak.

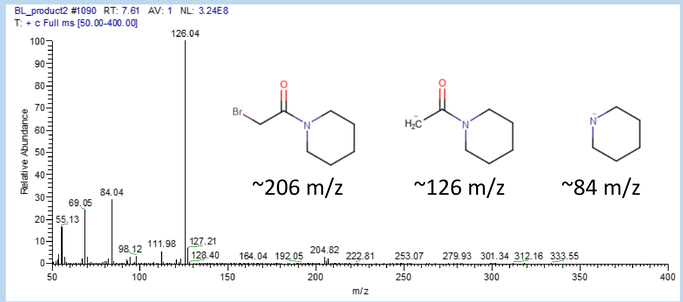


Figure 3: MS from the amination of the 3,5-dibromosalicylaldehyde. This product eluted at 7.47 minutes in the GC in addition to a peak at 9.25 minutes for an alternative product.

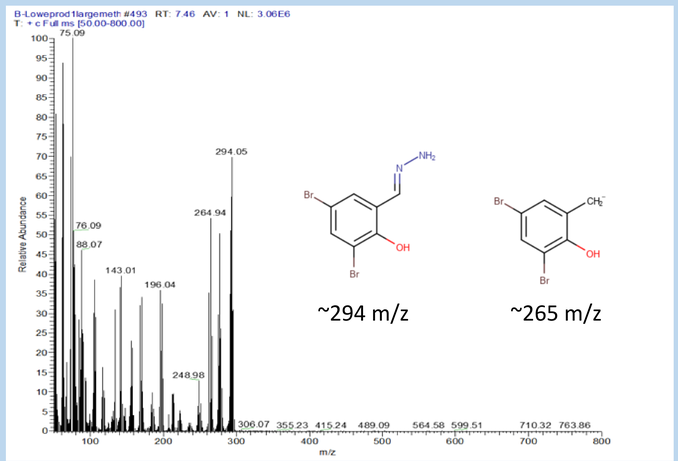


Figure 4: MS from the amination of the salicylaldehyde. This product eluted at 4.08 minutes in the GC as a sharp, lone peak.

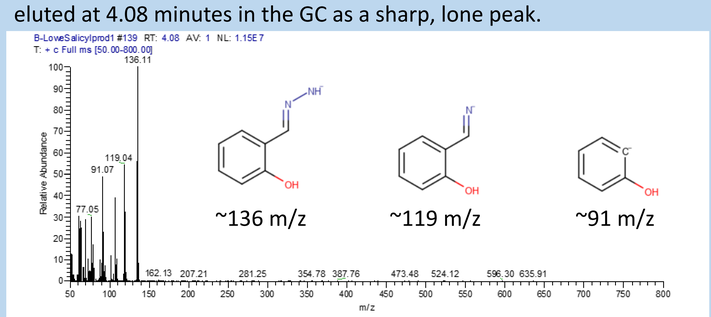
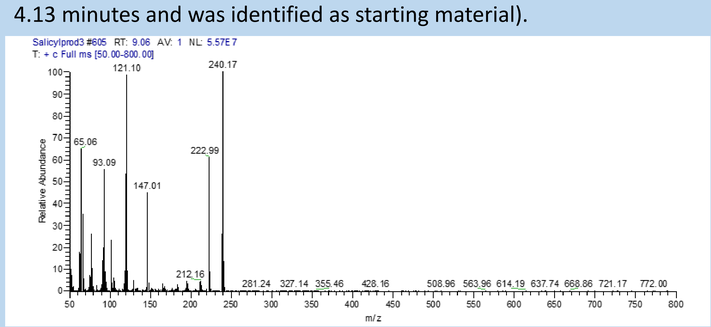
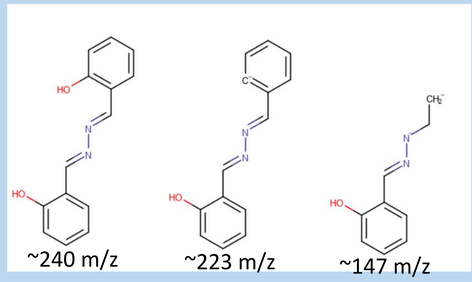


Figure 5: MS from the failed salicylaldehyde substitution reaction. This product eluted at 9.06 minutes as one of two peaks (the other eluted at 4.13 minutes and was identified as starting material).



Discussion

Figure 6: The presumed fragments from the MS in figure 5. A GC/MS library search helped identify this alternative product as a salicylaldehyde hydrazone dimer



Unfortunately, the desired, completed peptoid monomers were not synthesized for either aldehyde. In fact, the third reaction was not completed for either aldehyde despite many attempts at running each reaction. The alternative product (left, Figure 6) of the salicylaldehyde hydrazone dimer was quite an intriguing find, but upon further examination, it was not a result of the addition reaction conditions. When looking back to the GC/MS spectrum of a scaled-up trial of the salicylaldehyde amination reaction (Scheme 1), there was a GC peak that eluted at 8.97 minutes and produced a MS spectrum nearly identical to that in Figure 5. This suggests that the dimer must form independently of reaction conditions.

While the successful completion of the third reaction for either substituent was not achieved, the ideas from this project could be drawn upon for further studies in the future. Perhaps using strictly dried solvents rather than stock solvents would allow the reactions to proceed with more success. The substituents chosen were plausible in theory but may also have brought with them some steric concerns which interfered in the reactions in ways that were not present in the reactions from previous research. The quest for a cis-inducing peptoid monomer certainly should continue as the possibility of increasing the proteomic toolbox can have major impacts in a variety of fields, including the pharmaceutical industry.[3]

Acknowledgements

I gratefully acknowledge the Biology and Chemistry faculty at St. Vincent College (especially Dr. Fish) for giving me the guidance and resources for this experiment, as well as teaching me the fundamentals that help make this research possible. Additionally, I extend a grateful acknowledgement to Dr. Caroline Proulx at NC State University for giving me significant background that assisted heavily in this experiment.

References

1. Sun, J.; Zuckermann, *ACS Nano* **2013**, *7*, 4715-4732
2. Proulx, C; Davern, C; Lowe, B; Rosfi, A; Ison, E, *Royal Society of Chemistry Chemical Science* **2021,** in progress
3. Gopalakrishnan, R., et al., *J. Med. Chem.* **2016**, 59(21) 9599-9621