COLLEGE OF SCIENCE
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THE HUNTINGTIN PROTEIN: ORGANIC SYNTHESIS OF POLY(GLUTAMINE) THROUGH SIDE CHAIN MODIFICATION OF POLY(GLUTAMIC ACID)

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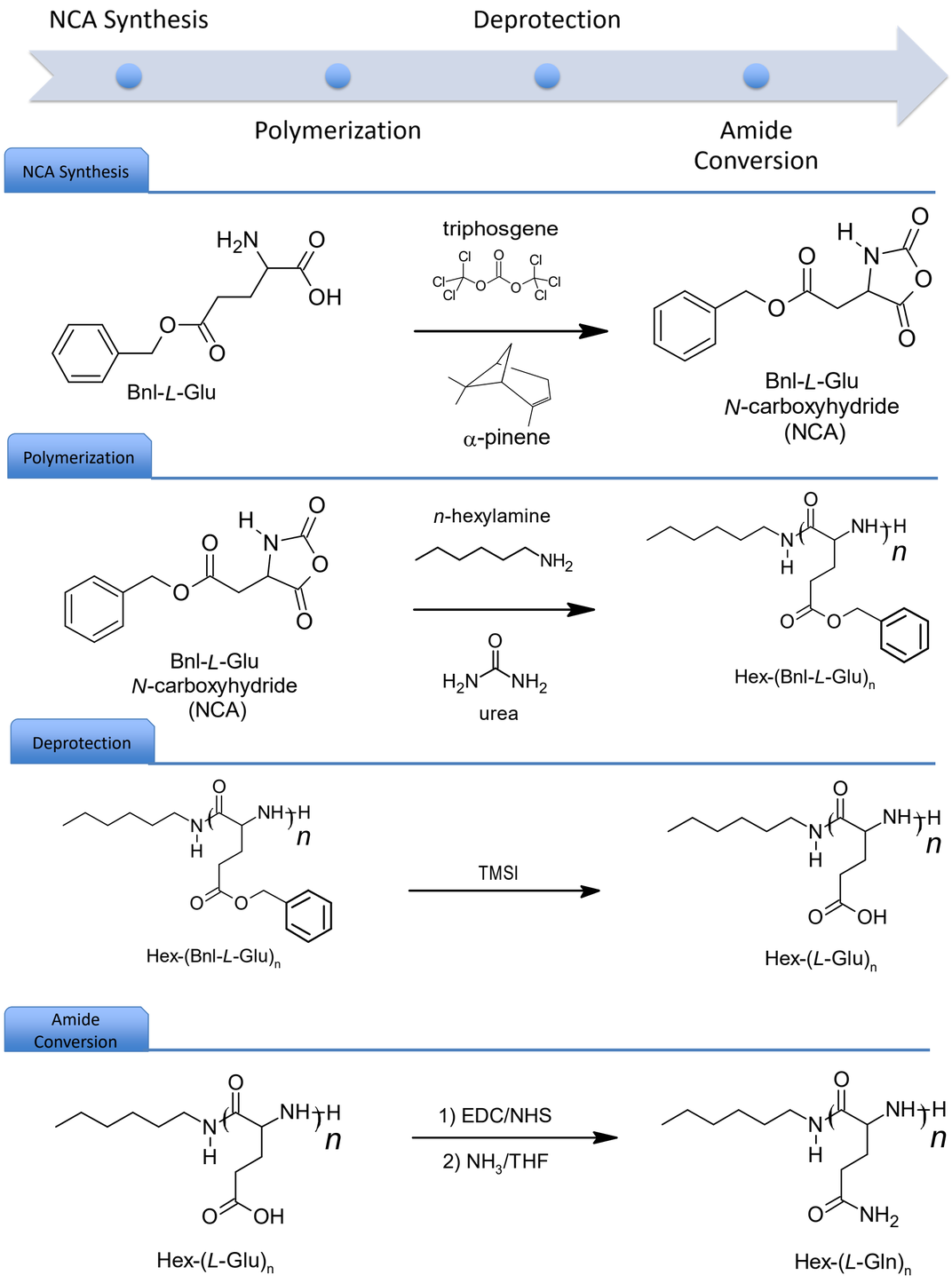
INTRODUCTION

- Huntington's Disease is a neurodegenerative disorder that causes loss of cognitive and physical abilities over time. This incurable, hereditary disease is caused by a mutation in one region of the Huntingtin protein (HTT) where there are numerous CAG trinucleotide repeat units that code for the amino acid Glutamine.
- Severity of the disease is directly correlated to the number of Glutamine repeat units:
  - Unaffected Stage: 6-35 Glutamine repeat units
  - Disease stage: 36+ Glutamine repeat units
- To fully understand Huntingtin's disease, one must:
  - synthesize poly(Glutamine) with pre-determined lengths
  - understand the physical behavior of poly(Glutamine)
- Well defined poly(Glutamic Acid) polymers were synthesized, polymer-analogous side chain conversions were investigated, and an NHS/EDC ester conversion proved successful.

METHODS



- Bnl-*L*-Glu was converted into an NCA (activated monomer)
- Using hexylamine as an initiator, Bnl-L-Glu-NCA was polymerized in varying chain lengths
- Polymers were deprotected using trimethylsilyl iodide (TMSI)
- Different polymer-analogous reactions were tested for the conversion of p(*L*-Glu) into p(*L*-Gln).

RESULTS

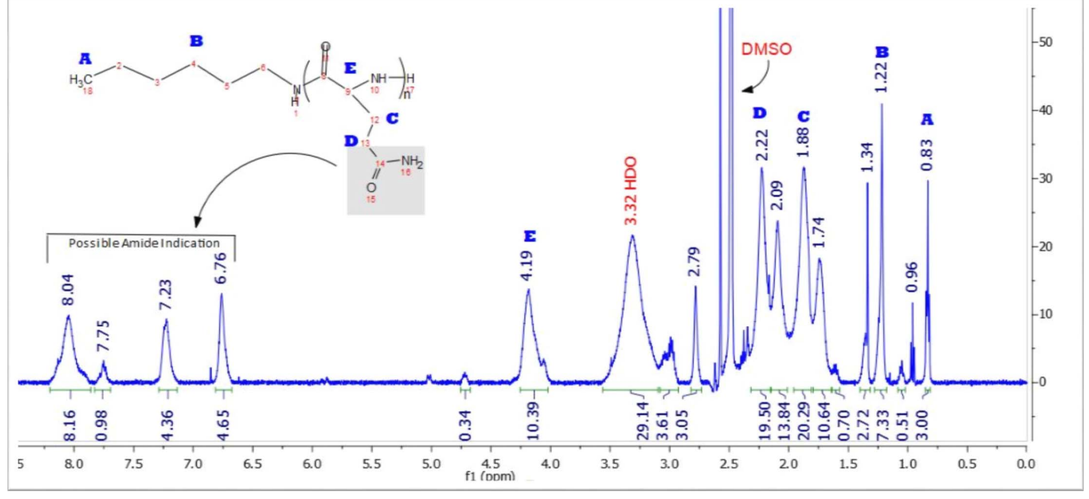


Figure 1: Hex-Glu10 Amide Conversion NMR Spectrum

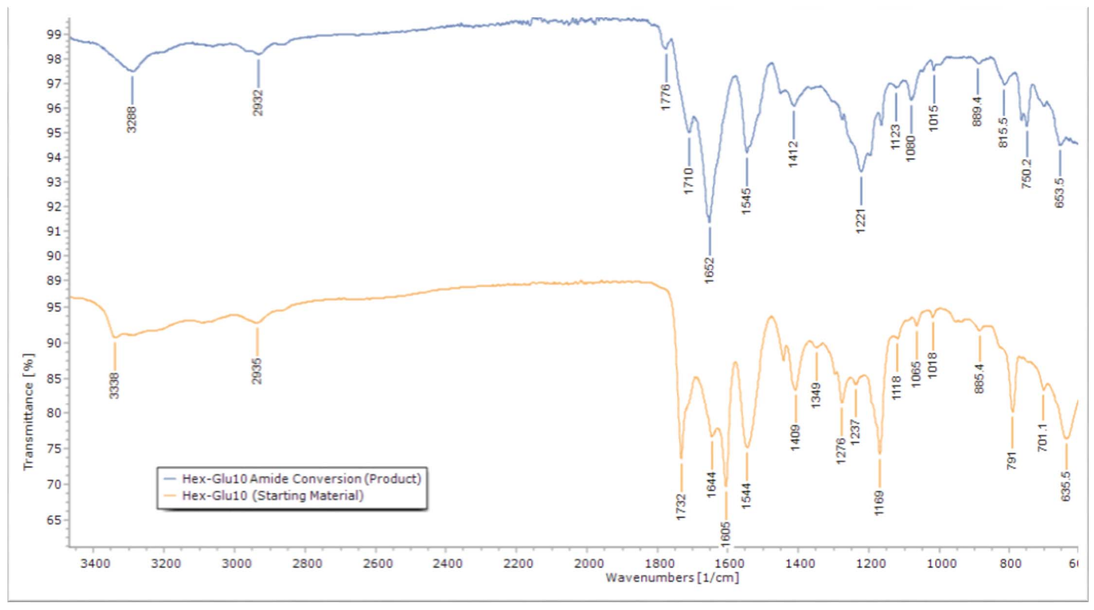


Figure 2: IR Spectra Comparison of Starting Material and Product Indicative of a Carbonyl Shift

CONCLUSIONS

- To conduct the amide conversion, four different esterification reactions were tested. The first reaction gave the best results.
  1. EDC/NHS → NH_3/THF
  2. EDC/NHS → NH_4/H_20
  3. EDC/NHS → TFE → NH_3/THF
  4. EDC/NHS → *p*-nitrophenol → NH_3/THF
- Since the only difference between starting material and end product is a change in the terminal functional group on the side chain, it proved to be very difficult to analyze.
- The difference in peak location between amide and carboxylic acid is very small, but there were several indications of a shift between starting material and product in the proton NMR and IR spectra pictured above.
- Another indication that the conversion occurred was the change in solubility of the starting polymer and the product. Before the conversion, the polymer was not soluble in water while the product was water soluble.
- In the future, the focus of this research will be on the esterification reaction that gave the best results. By manipulating certain conditions, the product yield and purity can be increased to create a more efficient process of synthesizing poly(Glutamine).

REFERENCES

Larson, A. M., Chen, J., & Klibanov, A. M. (2013). Conjugation to Polymeric Chains of Influenza Drugs Targeting M2 Ion Channels Partially Restores Inhibition of Drug-Resistant Mutants. *Journal of Pharmaceutical Sciences,102*(8), 2450-2459. doi:10.1002/jps.23644

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