

Side-Chain-Directed Chiral Sorting in 24-Atom Triazine Macrocycles

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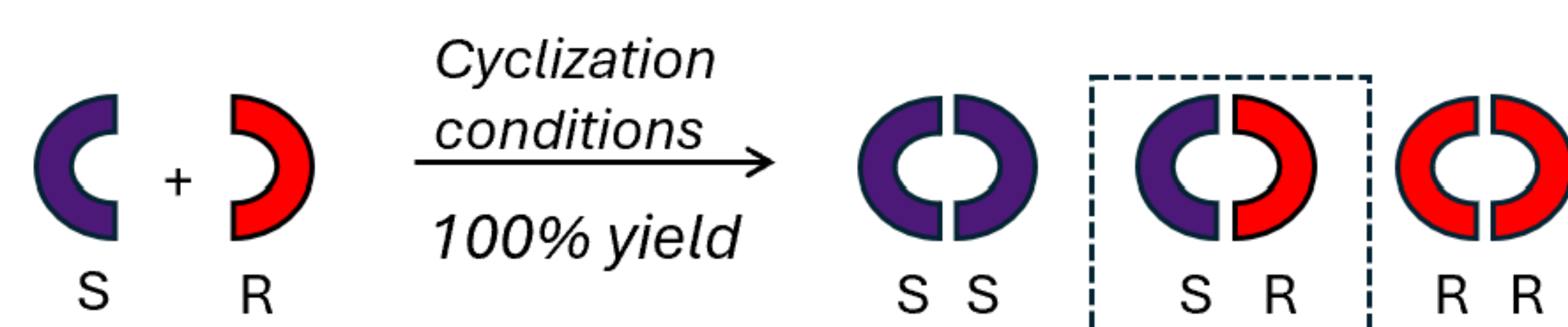


Research Question

How does the absolute configuration of amino acid side-chains affect chiral sorting in 24-atom triazine macrocycles?

Design

Monomers bearing chiral sidechain will be subjected to the cyclization conditions and the resulting products evaluated by ^1H NMR spectroscopy. If chiral sorting occurs, a deviation from the statistical product mixture (1:2:1) should be observed. Preference for heterodimers is desirable.

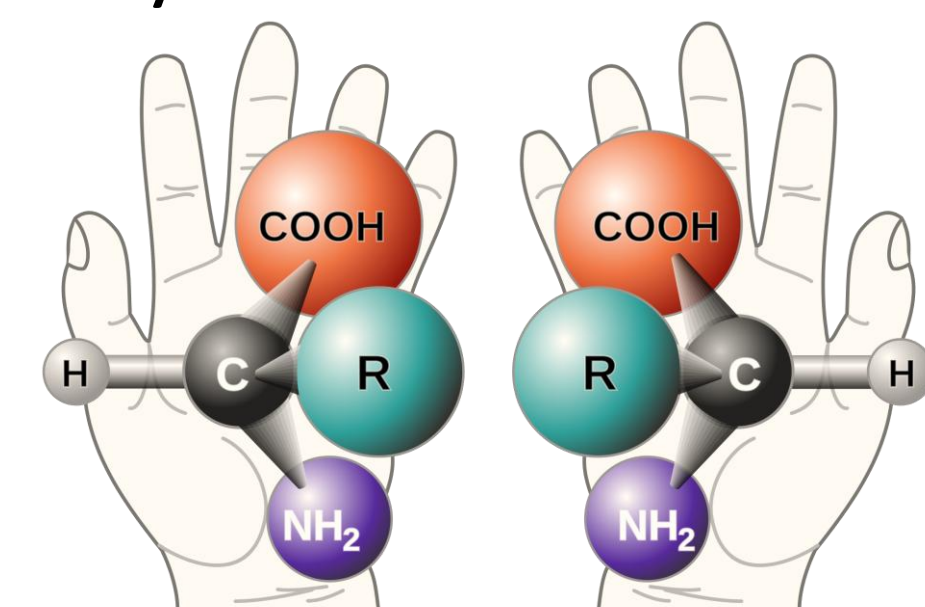


Abstract

Triazine macrocycles derived from two monomers undergo quantitative cyclization. These monomers comprise a central triazine ring bearing a protected hydrazine group and an amino-acid linked acetal. Choosing amino acids with large sidechains affords an opportunity to induce sorting. NMR and crystallographic studies suggest that valine and isoleucine favors chiral sorting, with only homodimers observed. Alanine and isovaline produce the expected statistical 1:2:1 distribution, suggesting the size of the branched side chain can influence stereochemical outcomes.

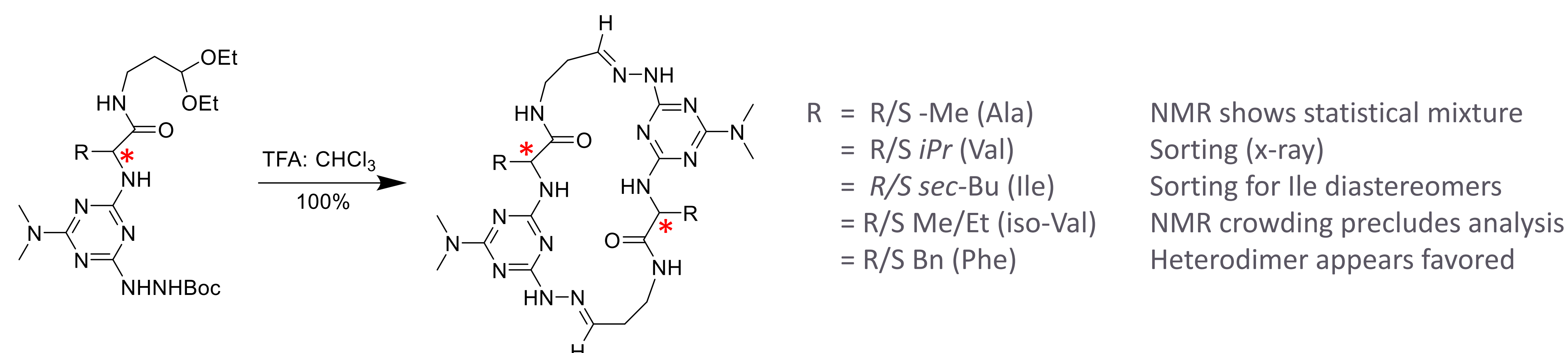
Why It Matters

Macrocyclic compounds are valuable scaffolds in medicinal chemistry due to their stability, selectivity, and ability to engage complex biological targets. Triazine macrocycles provide a platform for examining how stereochemistry influences macrocycle assembly.



Because biological systems are inherently chiral, homochiral and heterochiral assemblies can exhibit different structural and functional behavior. Here, chiral sorting in 24-atom triazine macrocycles derived from S- and R-branched amino acids is investigated.

Macrocyclization Targets and Preliminary Results



Crystallographic and NMR Evaluation of Macrocycles

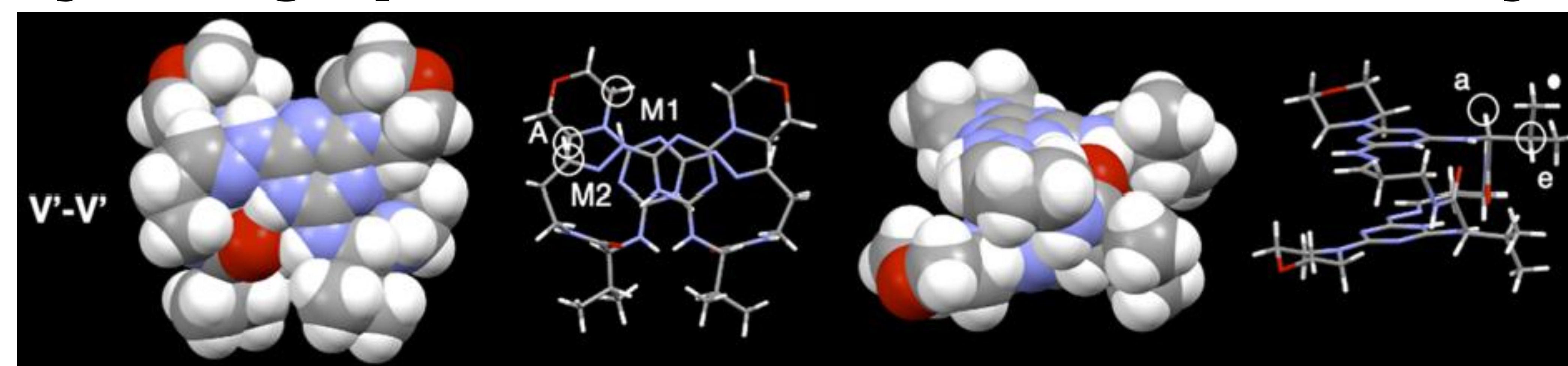


Figure 1. Crystal structure of morpholine analog, V-V, showing the proximity of the sidechains. The crystal structure shows both enantiomers in a single unit cell.

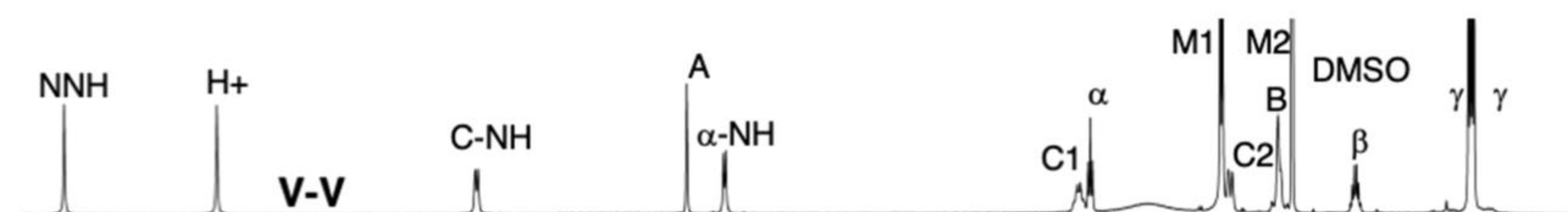


Figure 2. The 400 MHz ^1H NMR of the valine macrocycle taken in $\text{DMSO}-d_6$ shows a single set of resonances consistent with enantiomers resulting from sorting.

Other Strategies for Characterization

CD spectra will be collected for both the macrocycle and the monomer to evaluate their chiroptical properties.

A polarimeter reading will be obtained for the macrocycle to quantify optical rotation.

HPLC will be explored to separate homodimer from heterodimer. Chiral HPLC will be explored to separate enantiomers.

Future Directions

Future work can examine chiral sorting in macrocycles formed from additional amino acids...

or...

the impact of the chirality at the auxiliary position on the triazine ring could be explored.

What's next for the undergraduates?

Abigail graduates in May with a degree in biochemistry and is pursuing [medical school](#).

Samantha is a junior intending to pursue a [Ph.D.](#) in chemistry.

Isabella graduates in May with a degree in chemistry and will work in the cosmetics industry as a [R&D chemist](#).

Lauren is a junior pursuing a degree in biology with plans to apply to [medical school](#).

Acknowledgements

The authors would like to acknowledge Texas Christian University College of Science and Engineering, specifically the Department of Chemistry & Biochemistry for support in this project. We also thank the NIH (R15GM139950) and the Robert A. Welch Foundation (P-0008) for support.

Contact for Questions about the PhD program, a visit, or science:

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Synthetic Scheme for the Preparation of Monomers – A Two Flask Process

