A route to libraries of triazine macrocycles using dynamic covalent chemistry: Application to engineering LogP

Gretel A. Stokes, Casey Patterson-Gardner, Eric E. Simanek*
Department of Chemistry, Texas Christian University, Fort Wort, Texas

DEPARTMENT OF Chemistry & Biochemistry
TCU COLLEGE OF SCIENCE & ENGINEERING

Introduction

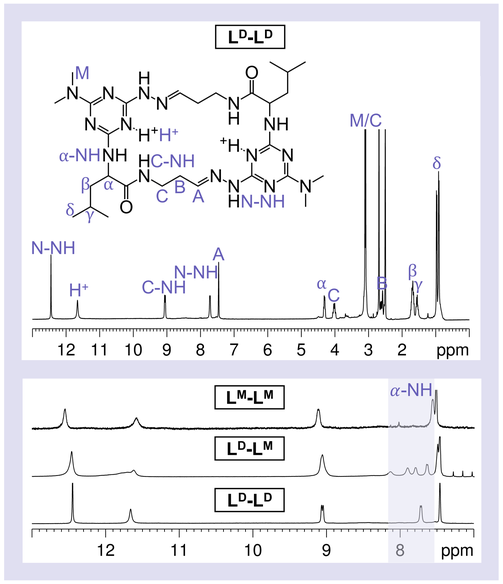
Macrocycles offer promising therapeutic potential in drug discovery, but understanding their design criteria, such as solubility properties, is still in its infancy due to synthetic challenges and the need for comparative analysis. This study aims to address these challenges by creating a library of 24-atom macrocycles to investigate and manipulate partition coefficients. Monomers—composed of a 1,3,5-triazine substituted with BOC-hydrazine, an acetal linked to the parent leucine through an amide bond, and various auxiliary amines—undergo quantitative dimerization upon treatment with acid. Four different auxiliary amines were utilized to produce four monomers, which were then combined and treated with acid to generate four homodimer and six heterodimer macrocycles. The octanol:water partition coefficients (logP) of the ten macrocycles ranges from 1.9 to 4.3. Furthermore, the logP values reveal a compensatory effect of substitution, where the heterodimers' partition coefficients fell between those of the corresponding homodimers at pH 7. This indicates that small molecular changes can lead to significant variations in the logP values of these macrocycles.

Research Goal

We designed a synthetic route to efficiently create a diverse library of 24-atom macrocycles with various R groups on their triazine rings. Commencing from four different monomers, we synthesized ten macrocycles through their dimerization. Our study focuses on exploring how these different R groups affect the logP of the macrocycles, aiming to use this as a predictor for the oral availability of our molecules.

Methods

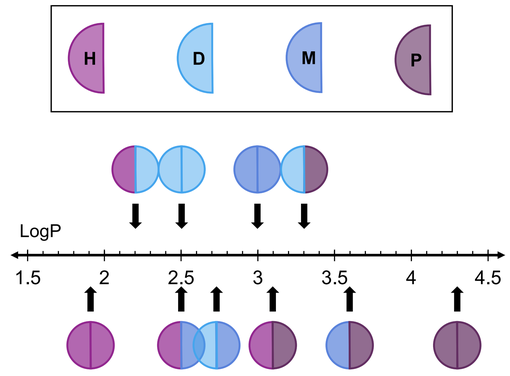
Reaction mixtures containing two monomers with different R groups yielded a mixture of two homodimer macrocycles and one heterodimer. For instance, mixing monomers '$\mathbf{L^D}$' and '$\mathbf{L^M}$' yields macrocycles '$\mathbf{L^D}$-$\mathbf{L^D}$', '$\mathbf{L^D}$-$\mathbf{L^M}$' and '$\mathbf{L^M}$-$\mathbf{L^M}$' in ratios that approximate the statistical expectation—1:2:1. This was confirmed by NMR spectroscopy of the macrocycle mixtures, which shows four equally-integrating peaks corresponding to the four distinct α-NH protons: two peaks for both protons on each homodimer and two peaks for the two inequivalent protons on the heterodimer.



LogP Results

The logP values of each macrocycle were measured to quantify its preference for partitioning between aqueous and organic phases. This assessment aimed to determine the effect of the R group on the relative partitioning between phases.

Below, circles represent the diverse macrocycles resulting from dimerization, with each half's color indicating the substituted R group. Positioned on the logP scale, they illustrate the measured logP values of each macrocycle.



Lower values of logP indicate an increase in polarity. At neutral pH, the data matches our intuition with polarity decreasing from substitution with **H** > **D** > **M** > **P**. Moreover, the logP of each heterodimer is a close approximation of the average of the two corresponding homodimers. That is $\mathbf{L^H}$-$\mathbf{L^H}$ and $\mathbf{L^M}$-$\mathbf{L^M}$ have logP values of 1.9 and 3.0 while the logP of the heterodimer $\mathbf{L^H}$-$\mathbf{L^M}$ is 2.5. Similarly, the logP values of $\mathbf{L^P}$-$\mathbf{L^P}$, $\mathbf{L^P}$-$\mathbf{L^H}$, and $\mathbf{L^H}$-$\mathbf{L^H}$ are 4.3, 3.1 and 1.9, respectively.

Conclusions

A library comprising ten macrocycles with diverse R groups substituted on their triazine rings was synthesized. The influence of the R group on partitioning between aqueous and organic media was quantitatively assessed through logP values. LogP values for homodimer macrocycles aligned with expectations based on their hydrophobicity: those with more hydrophobic R groups displayed higher logP values. Heterodimer macrocycles demonstrated compensatory effects of R group substitution, with their logP values falling between those of the respective homodimers.

Future Work

The library synthesis will expand to include glycine-based macrocycles with additional auxiliary amines, allowing for investigation of their effects on logP values. Moreover, efforts will be made to optimize the synthetic route to minimize purification time. Currently, purification of monomers involves column chromatography. A new synthetic route is being developed, using the ethyl ester of the amino acid, which undergoes a trans-acylation reaction to yield the amide-linked three-carbon acetal. Recently, pure monomers synthesized using this method required purification only via extraction.

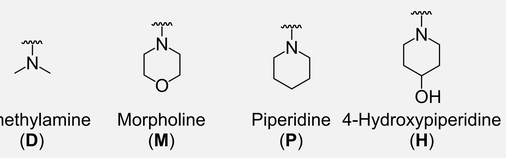
Acknowledgements

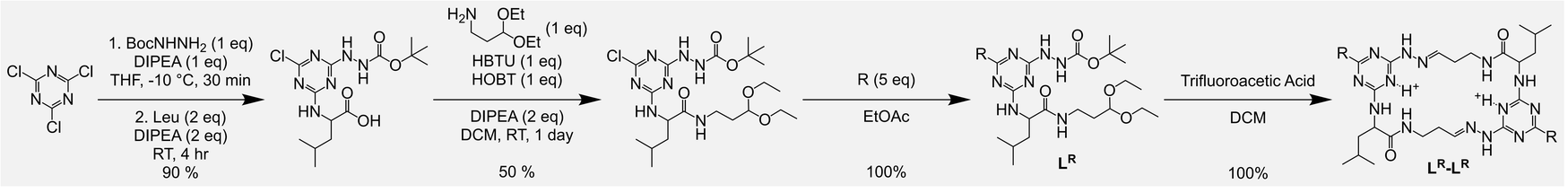
We thank the Robert A. Welch Foundation (P-0008) and the NIH (R15GM135900) for support.

Synthetic Route to a Library of Macrocycles

A trichlorotriazine is substituted with BOC-hydrazine, a 3-carbon acetal tethered as an amide to leucine, and various auxiliary amines. Combining four monomers, denoted $\mathbf{L^R}$, where R represents a unique moiety (pictured right), results in ten distinct macrocycles, denoted $\mathbf{L^R}$-$\mathbf{L^{R'}}$, upon dimerization.

R Groups:





References

1. Capelli, R., Menke, A. J., Pan, H. J., Janesko, B. G., Simanek, E. E., & Pavan, G. M. (2022). Well-Tempered Metadynamics Simulations Predict the Structural and Dynamic Properties of a Chiral 24-Atom Macrocycle in Solution. *ACS OMEGA*, *7*(34), 30291-30296. https://doi.org/10.1021/acsomega.2c03536
2. Yepremyan, A., Mehmood, A., Asgari, P., Janesko, B. G., & Simanek, E. E. (2019). Synthesis of Macrocycles Derived from Substituted Triazines. *CHEMBIOCHEM*, *20*(2), 241-246. https://doi.org/10.1002/cbic.201800475
3. Falorni, M., Giacomelli, G., Mameli, L., & Porcheddu, A. (1998). New 1,3,5-triazine derivatives as templates for the homogeneous phase synthesis of chemical libraries. *Tetrahedron Letters*, *39*(41), 7607-7610. https://doi.org/https://doi.org/10.1016/S0040-4039(98)01654-2

Contact Information

gretel.jordan@tcu.edu
e.simanek@tcu.edu