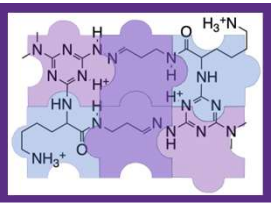

Isomer Evaluation in Triazine Macrocycles: Implications for Drug and Materials Design

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Take-away

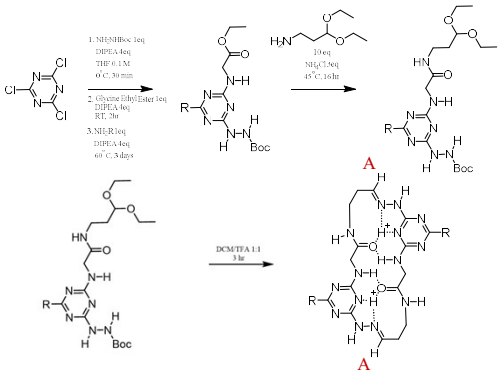
Instead of 1 conformation for 1 drug-like molecule, this system gives… 7+ conformations for 1 drug-like molecule, increasing the likelihood of finding a drug lead.

Abstract

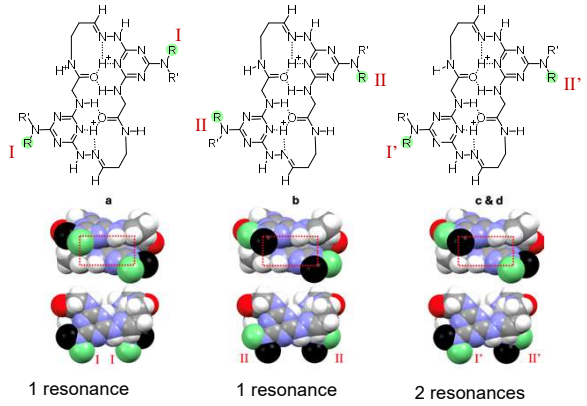
Macrocyclic molecules are a target for drug studies due to their larger structures that allow for interactions with larger molecules. Two macrocycles with differing auxiliary amine side chains were synthesized in five steps with isolable intermediates that can be purified and characterized. The choice of isobutylamine as an auxiliary group reflects a desire to study macrocycles that mimic the structures of amino acids due to their implications in potential drug synthesis. N-methylbenzylamine was chosen for further evaluation of macrocycles with asymmetrical auxiliary amine side chains. Characterization of macrocycles with asymmetrical auxiliary amine side chains show the presence of rotational isomers that are well-defined and present in predictable ratios, as shown by ^{1}H NMR spectroscopy.

Build macrocyclic molecules for rotamer evaluation.

1. Versatile inexpensive building blocks groups that, one, allow for the formation of a macrocycle and, two, emulate amino acids, are instilled in a series of reactions, forming a monomer.
2. The monomer dimerizes to form a symmetrical macrocycle at 100% yield.
3. The macrocycle is then evaluated by NMR spectroscopy to show different rotamer conformations.

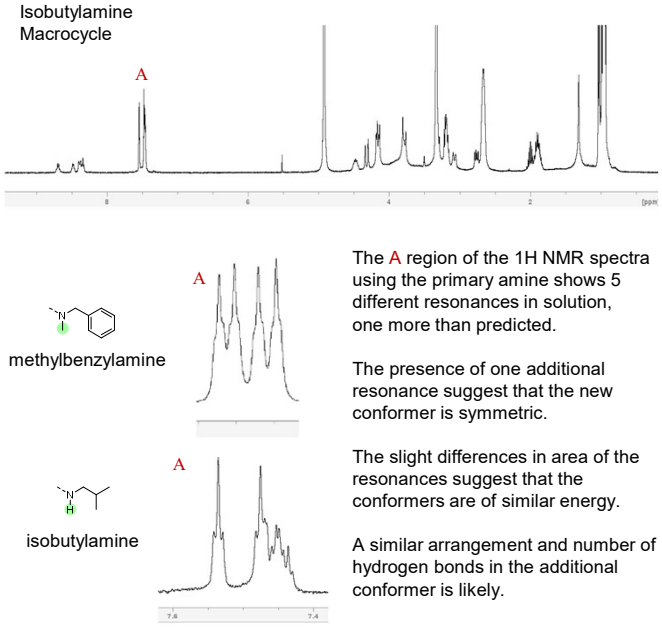


Three isomers are predicted.



The folded structure of the macrocycle creates four different environments. Two are symmetric predicting one resonance each in the ^{1}H NMR spectra, one is asymmetric giving two resonances. Although I and I' could be similar, fortunately, they might be resolved in the NMR spectra.

NMR spectra show 3+ isomers.



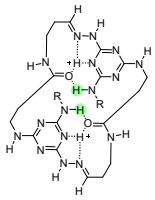
The A region of the 1H NMR spectra using the primary amine shows 5 different resonances in solution, one more than predicted.

The presence of one additional resonance suggest that the new conformer is symmetric.

The slight differences in area of the resonances suggest that the conformers are of similar energy.

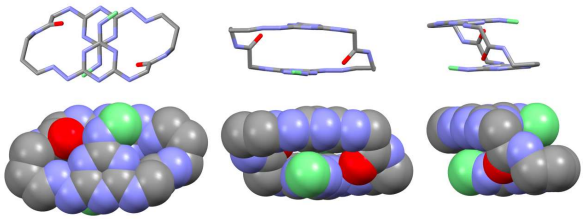
A similar arrangement and number of hydrogen bonds in the additional conformer is likely.

A new conformer is assigned for the primary amine.



A new conformer where protonation occurs opposite the amino acid (instead of opposite the auxiliary amine) creates a similar pattern of hydrogen bonds and a geometry where the auxiliary amines are oriented differently.

This conformation is observed in a crystal structure obtained for a related compound.



A single additional resonance requires a single symmetric environment in the new conformer. To access an asymmetric macrocycle requires the loss of a hydrogen bond, which is energetically unfavorable.

While the asymmetric macrocycle may be persistent, energetics would dictate that it would exist in a small population, below the NMR limits of detection.

What's next for these researchers?

Annie – Annie is a 3rd year student who has been working in the laboratory for 3 months. She plans to pursue a PhD when she graduates.

Liam Claton is a third-year graduate student who supervised our work in the lab. He hopes to return to Minnesota for a postdoctoral appointment, or start a company based on this work.

Dissemination

This research was presented at ACS 2025 Spring Convention. It is up for publication in The Journal of the American Chemical Society.

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