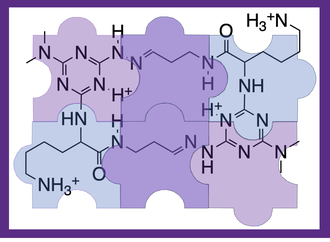

Marcocycles: the Chemical Chameleons

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Take-away

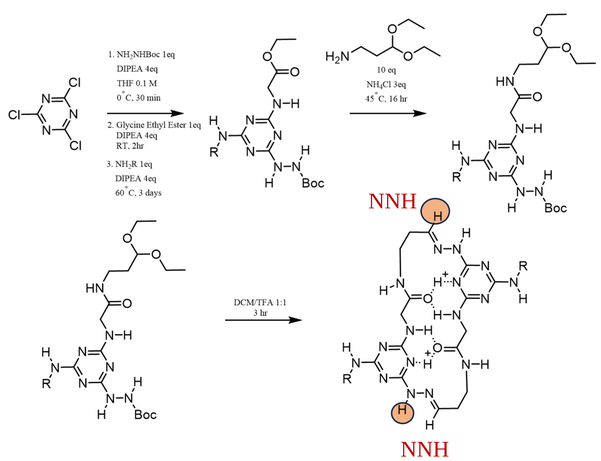
Instead of 1 conformation for 1 drug-like molecule, this system gives… 7+ conformations for 1 drug-like molecule, increasing the likelihood of finding a drug lead.

Abstract

The disappearance (and emergence) of complexity is a useful tool for evaluating molecular structure. For macrocycles comprising [s]-triazines, hindered rotation about the triazine-N bond leads to the appearance of isomers on the NMR timescale. For acyclic intermediates comprising a symmetric auxiliary amine, evidence for all four rotational isomers (rotamers) is observed. The 1H NMR spectrum is complex. Upon cyclization, a single isomer emerges. The 1H NMR spectrum resolves, and subunit symmetry is revealed in these dimers. When the symmetric auxiliary amine--a secondary amine such as dimethylamine, piperidine or morpholine--is replaced with a primary amine, complexity is reintroduced. Macrocycles appear as a distribution of rotamers. Here, strategies for evaluating isomer distribution are reported. Isomer assignment is attempted. The implications for drug and materials design are described.

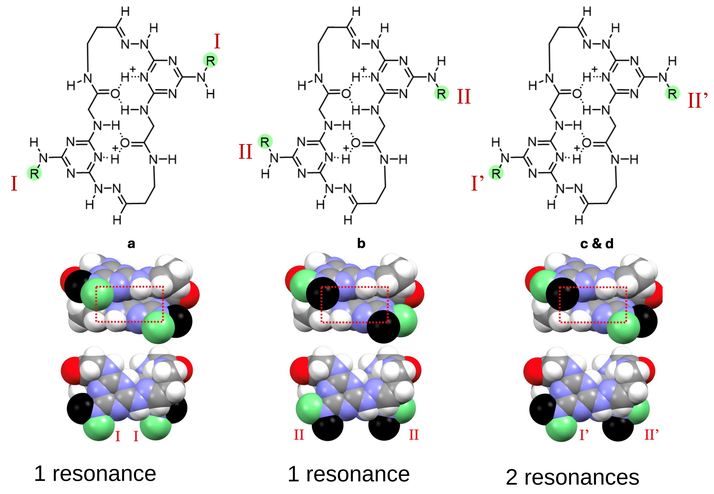
Build macrocyclic molecules for rotamer evaluation.

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.



R = benzylamine

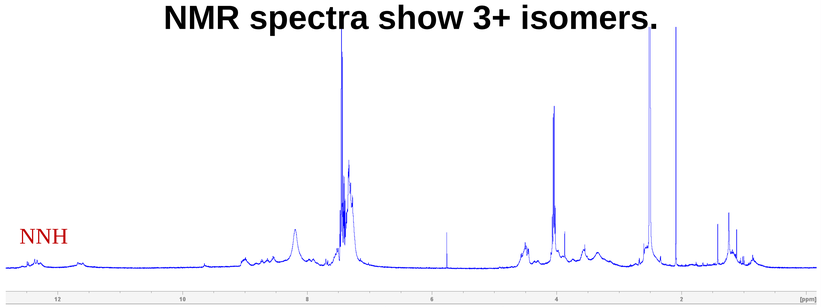
Three isomers are predicted.



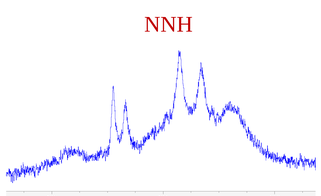
1 resonance | 1 resonance | 2 resonances

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 NNH region of the 1H NMR spectra shows 5 different resonances in solution, one more than predicted.



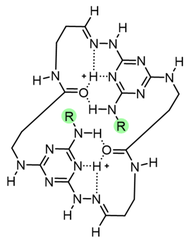
The presence of one additional resonance suggest that the new conformer is symmetric.

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.

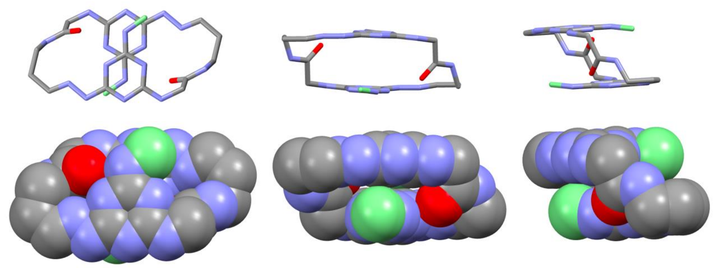
The NNH region for the benzylamine macrocycle has conflicts with the benzylic protons, but many resonances can be seen in the NH and NNH regions

A new conformer is assigned.



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 this undergraduate?

Amarige – Amarige is a 3rd year student who has been working in the laboratory since 2023. She plans to attend medical school after graduation.

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.

This work is supported by the National Institutes of Health (R15 GM 135900) and the Robert A. Welch Foundation.

A special thanks to the DFW Local Section of ACS for supporting travel expenses for this research group.

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