The effects of protonation and hydrogen bonding on templating efficient macrocyclization

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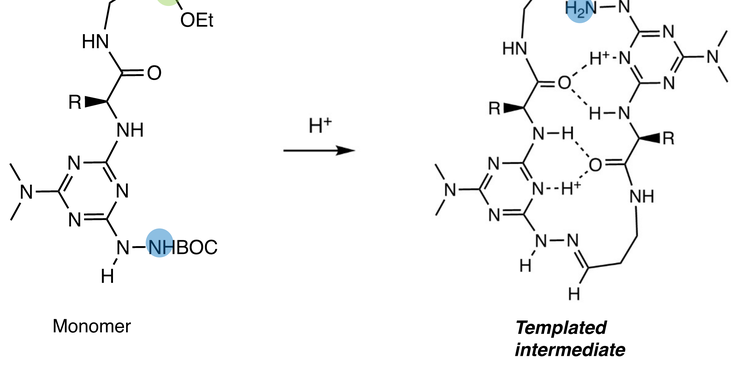
Introduction

Macrocyclic drugs adopt multiple conformations--a behavior referred to as chameleonicity--to navigate hydrophobic cellular membranes and aqueous intracellular environments. The rules for understanding this behavior are beginning to emerge through the study of existing drugs like cyclosporine or the synthesis of model systems. Historically, one challenge to macrocycle synthesis is low yield reactions. To this end, dynamic covalent chemistry has been explored. Here, macrocycles are afforded readily by dimerization with the formation of two hydrazones.

The efficiency of the macrocyclization reaction led to the hypothesis that upon formation of the first hydrazone, the acyclic intermediate was preorganized to place the hydrazine and acetal in close proximity thereby reducing the likelihood of oligomeric or polymeric products. The preorganization could result from a network of hydrogen bonds. Moreover, in an acidic environment, wherein the triazine ring is protonated, the opportunity for bifurcated hydrogen bonds emerge. Computation has been used to identify sites for protonation and the energetic contributions of hydrogen bonding.

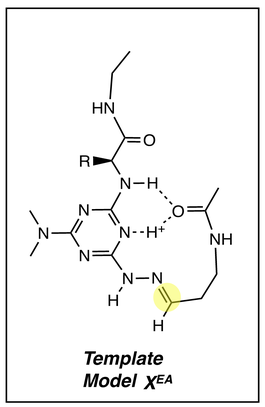
To explore templating and the role of protonation in the formation of hydrogen bonds, model systems were prepared that emulate 'half' of the macrocycle. The acetylated aminoacetal offers a well-resolved NMR spectrum. In contrast, hindered rotation about the triazine-N bond leads to a mixture of rotamers in the hydrazine component. However, upon condensation, a single rotamer is observed and resonances corresponding to the hydrogen bonded protons emerge downfield between 7-12 ppm. Computation provides estimates of the energetic contribution of the bifurcated hydrogen bond.

Quantitative cyclization based on a hydrogen bonded template



Monomer

Templated intermediate

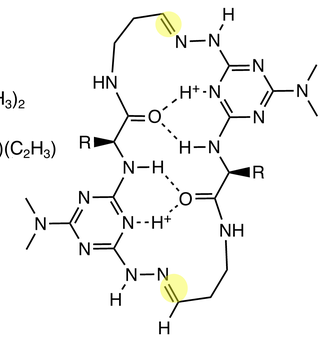


Template Model X^{EA}

G-G, G^{EA} R = H

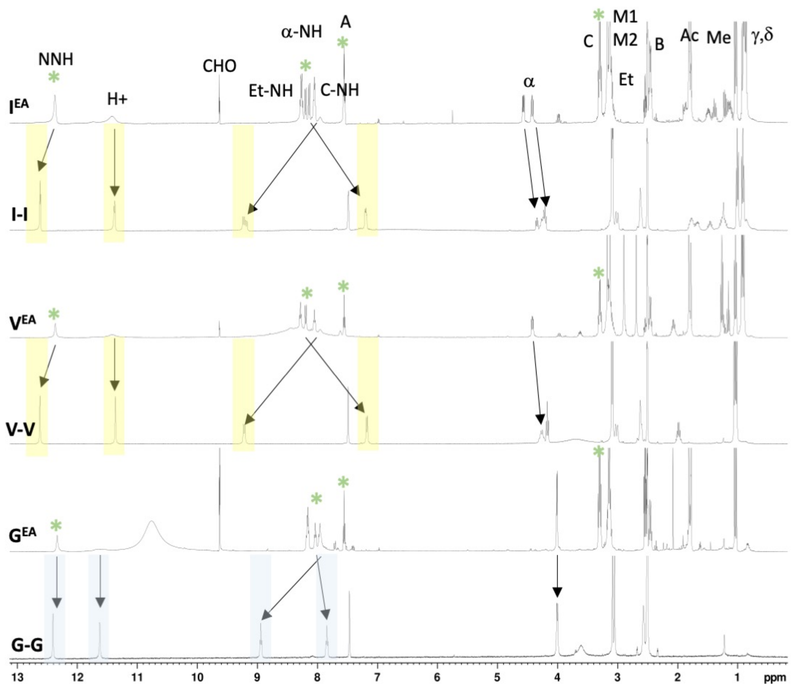
V-V, V^{EA} R =$CH(CH_3)_2$

I-I, I^{EA} R = $CH(CH_3)(C_2H_3)$



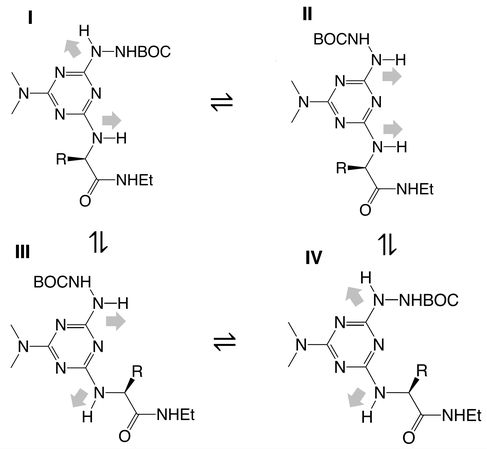
Simple Acyclic Models Recapitulate Preorganization

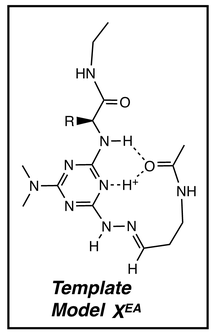
Well resolved-resonances apparent in the downfield region of the ^{1}H NMR spectra of macrocycles and acyclic models demonstrate hydrogen bonding interactions.



Loss of Spectral Complexity upon Hydrazone formation results from rotamer selection

Rotamer **I** only is observed in the macrocycles. The acyclic models were used to show that favoring of one species could be attributed to hydrogen bonding interactions.





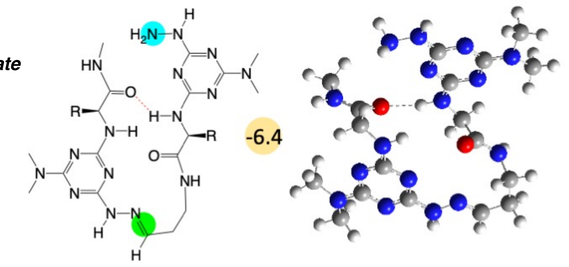
Template Model X^{EA}

Increasing number of hydrogen bonds stabilizes preorganized intermediates

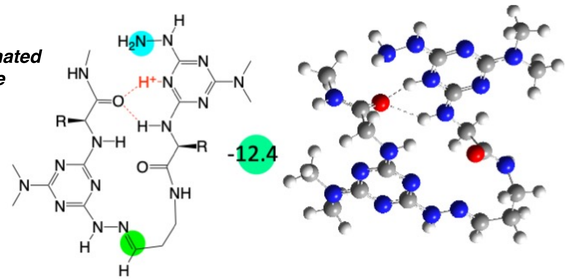
DFT calculations show proposed intermediate afforded four hydrogen bonds with greatest stabilization energy, 14.2 kcal/mol

Favored

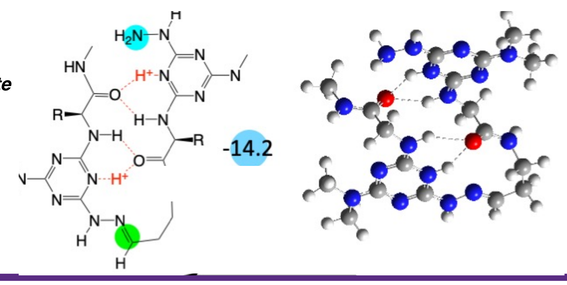
Neutral intermediate



Monoprotonated intermediate



Proposed intermediate



Conclusions & Future work

- Upon hydrazone formation, a network of hydrogen bonds forms in the molecule and the number of rotamers is decreased.
- Experimental and computational evidence validates a model for templated cyclization.
- Further studies can be conducted to determined if amino acid choice affects quantitative yields and stabilization energy of hydrogen bond network.

References

Menke, A. J., Henderson, N. C., Kouretas, L. C., Estenson, A. N., Janesko, B. G., & Simanek, E. E. (2023). Computational and Experimental Evidence for Templated Macrocyclization: The Role of a Hydrogen Bond Network in the Quantitative Dimerization of 24-Atom Macrocycles. *Molecules 28*(3), 1144. https://doi.org/10.3390/molecules28031144

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