Exploring Cyanuric Chloride Chemistry to Synthesize Macrocycles of Different Sizes

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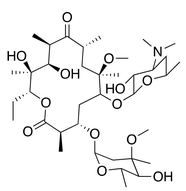
Abstract

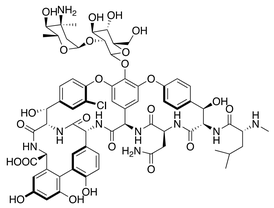
In chemistry, cyclic compounds of twelve or more members including any hetero-atom are considered macrocycles. Many bioactive natural products containing macrocycles have been isolated and synthesized. Some of the macrocyclic antibiotics that have been found or synthesized are vancomycin, daptomycin, polymyxin, bacitracin A and azithromycin. Construction of macrocycles is usually considered a challenging step in the synthesis. Here, we represent synthesis of different sized macrocycles by connecting two or more cyanuric chloride molecules substituted with various length amino acids to give rings of different sizes. So far, we have been able to synthesize macrocycles of 22, 24, 26, and 28 members by forming of dimers. Our goal to influence that the length of carbon chains has on ring formation as well as the solubility of these molecules.

Background

The formation of macrocycles by ring-closure is called macrocyclization. Ring closing reactions do not favor the formation of large rings. Instead, polymers tend to form. Macrocycles have been a topic of research for decades due to their biological activity, topology, and as tests of the limits of synthetic methodology. Some classes of macrocycles are relatively easy to synthesize, while others present challenges. Antibiotics vancomycin, fidaxomicin, nisin, azithromycin, and clarithromycin contain different sized macrocycles.

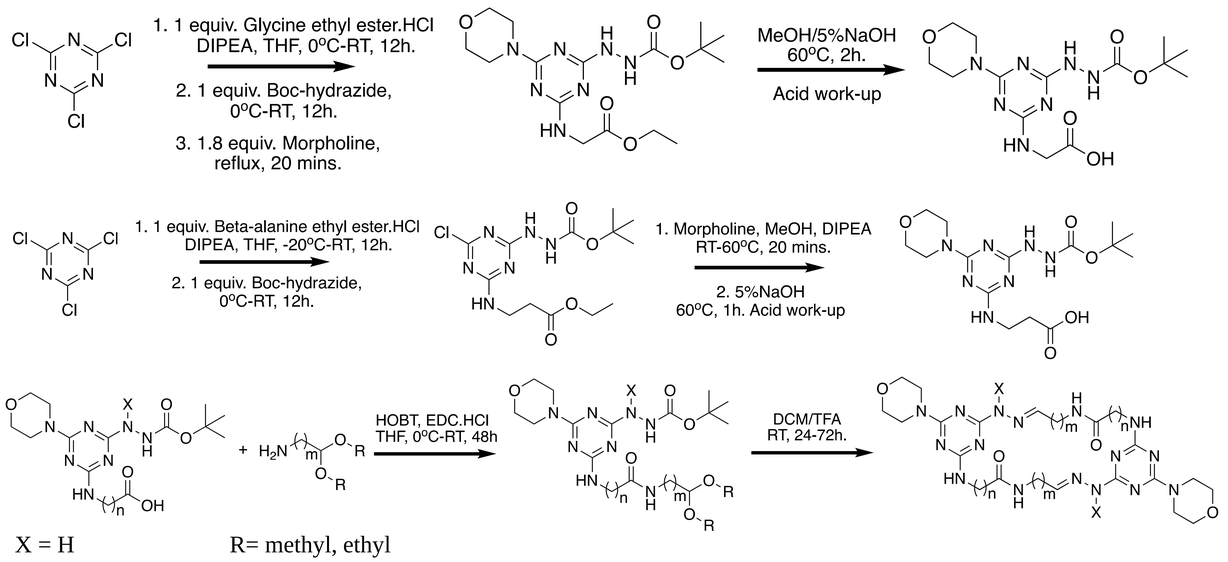


Clarithromycin



Vancomycin

Synthetic Schemes



X = H

R= methyl, ethyl

Results and Characterization

Macrocycles	n	m	Ring Size
1	1	1	22
2	1	2	24
3	1	3	26
4	2	1	24
5	2	2	26
6	2	3	28

Table 1: List of macrocycles synthesized. (X = H)

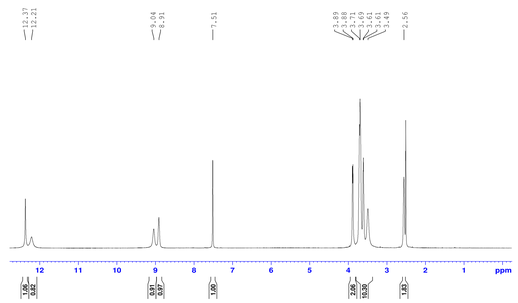


Figure 1: ^{1}H-NMR of macrocycle (M-2)

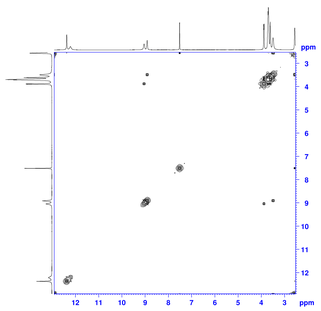


Figure 2: ^{1}H-COSY of macrocycle (M-2)

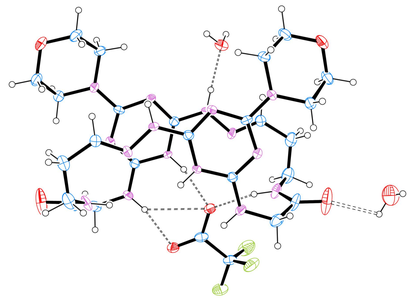


Figure 3: X-Ray crystal structure of M-2

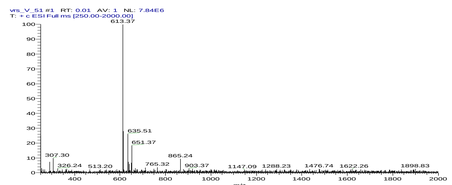
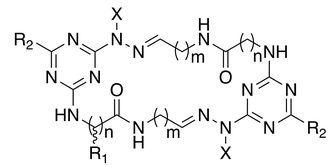


Figure 4: Mass spectrum of M-2.
Expected; m/z 612.31.
Observed; 613.37

Future Plans

The future plan for this research is to expand the library of homodimer macrocycles to include different sizes and eventually heterodimers. The interior of the ring could recognize guest molecules or metal ions opening the possibility of using these macrocycles to carry medicines. Solubility of these macrocycles has been challenge so far. To enhance the solubility, morpholine could be replaced with hydrophilic groups such as 4-aminopiperdine. After a sufficient amount of unique macrocycles are acquired, the molecules will be put through a high throughput screen to see if they can interfere with protein-protein interactions, thus acting as drugs in their own right.

Some of the planned macrocycles are shown below.



X = CH_3
R_1 = isopropyl
R_2 = 4-aminopiperdine

References:

- Hamilton-Miller, J. M. *Bacteriol. Rev.* **1973**, *37*, 166-196

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