EXPLORING THE IMPACT THAT S-OXIDATION HAS ON CONFORMATION AND SOLUBILITY OF A METHIONINE MACROCYCLE

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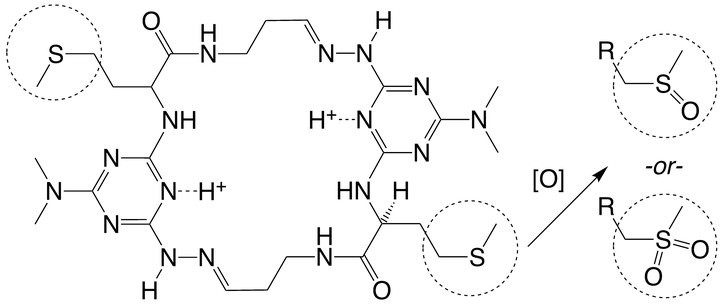
LONG TERM GOAL

The long-term goal of this research is to develop new drugs that could be adopted by the pharmaceutical industry for any number of different diseases. Macrocyclic drugs have been used clinically for decades. These drugs adopt multiple conformations to navigate both hydrophobic and aqueous environments. Therapeutic intervention requires that macrocycles remain flexible to facilitate the adoption of these different conformations. The ability to perform these contortions is predicted by logP, an octonal:water partition coefficient. Macrocycles (as well as small molecule drugs) that are suitable for oral delivery have a logP value <5.

Macrocycles may differ in chain length, amino acid, and/or the auxiliary group. Each molecule is unique in that these differences change the solubility of the molecule. In addition, some macrocycles share similar conformations despite their difference in composition. Understanding both the structure and solubility of these different macrocycles is paramount in synthesizing potential drugs for pharmaceutical industries.

THIS PROJECT

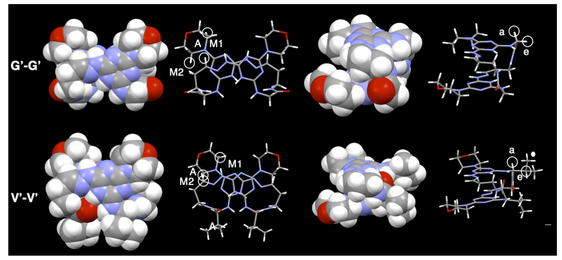
While methionine is under-represented in proteins, it is enriched significantly at protein-protein interaction sites. The study commences with the synthesis of a macrocycle with an auxiliary group that allows for solution-phase NMR analysis. Using a model that predicts the solution structure of 24 atom macrocycles, the solution phase structure can be determined. Upon formation, the macrocycle undergoes an oxidation reaction to the sulfoxide derivative. This macrocycle is of interest because the impact that oxidation has on logP has not been reported. Additionally, S-oxidation could change the conformation of the molecules.



PREDICTIVE MODEL: SOLUTION PHASE STRUCTURE

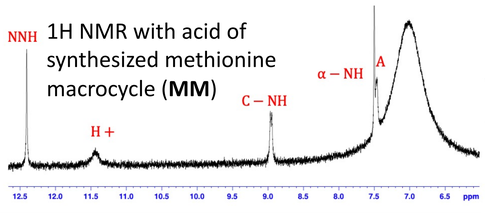
Shared characteristics of our macrocycles:

1. Efficiency of macrocyclization
2. Common NMR features
3. C2 symmetry in solution
4. An (E)-hydrazone
5. A common site for protonation
6. A common rotamer state
7. Folded conformations in solution and the solid-state

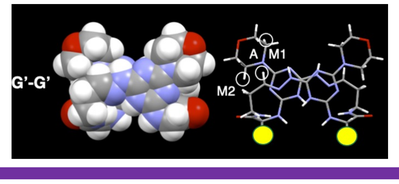


G'-G' equatorial protons do not interact with one another and the triazine rings stack upon the hydrazones
V'-V' sidechains do interact, and congestion leads to pi-pi stacking with greater overlap of the triazine rings

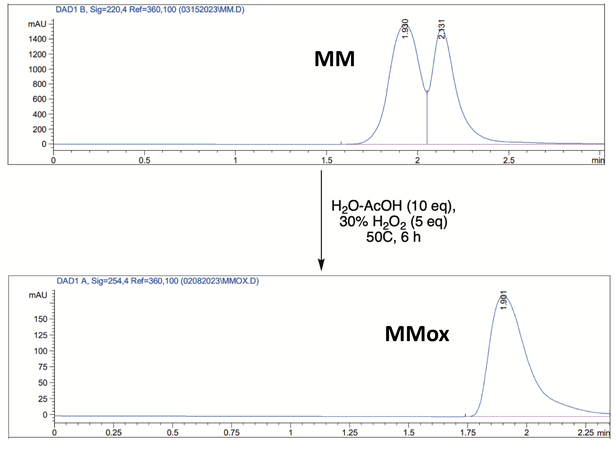
NMR SHIFT COMPARISONS SHOWS MM ADOPTS A SHAPE LIKE GG



Characteristic	G-G	M-M	V-V
δ^1H NNH (ppm)	12.41	12.41	12.62
δ^1H H+ (ppm)	11.63	11.43	11.36
δ^1H C-NH (ppm)	8.94	8.95	9.22
δ^1H A (ppm)	7.47	7.46	7.49
δ^1H α-NH (ppm)	7.84	7.47	7.18
δ ^{13}C C=O (ppm)	171.9	172.2	173.4
δ ^{13}C A (ppm)	148.4	142.3	148.4



OXIDATION DRAMATICALLY CHANGES LOGP



	GG	TT	AA	YY	PP	MM	VV	II	FF	LL	MM(ox)
logP	-6.6	-4.1	-1.9	-1.9	-1.5	0.3	0.4	1.6	1.6	1.8	Between 0 and 5

CONCLUSION & FUTURE WORK

- MM engages in pi-pi stacking between the triazine rings and hydrazones
- MM displays similar NMR features to GG with some nuanced elements
- S-oxidation increases hydrophilicity (logP)
- Obtain crystal structures upon synthesis of methionine macrocycle with morpholine auxiliary group to promote x-ray crystallization
- Obtain the mass spectrum of the oxidized methionine macrocycle for analysis

ACKNOWLEDGMENT

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