Exploration of the Geometric Isomers of Cyclic Sulfones

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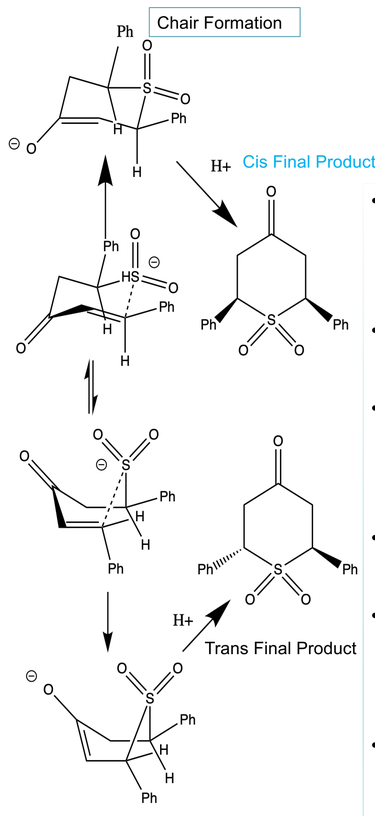
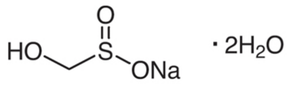
Introduction



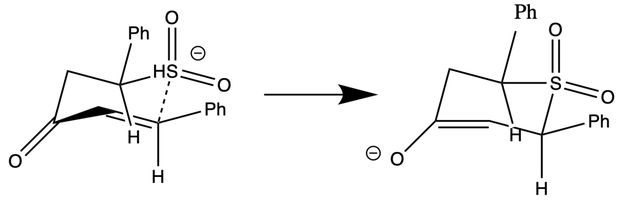
Boat Formation



Rongalite

- Rongalite is a very useful reagent in organic synthesis and can easily create sulfones, sulfides, and sultines, or can make the reactant undergo dehalogenation or reduction.
- Dr.Bebbington has been working with rongalite to synthesize substituted cyclic sulfones.
- Recently he has also observed the trans-isomer to be the major product in his experiments despite it being less thermodynamically stable than the cis-isomer
- The formation of the trans-isomer of the substituted cyclic sulfone is kinetically favored in the reaction
- The goal is to use computational methods to understand why the the trans-isomer is kinetically favored and therefore the major product in the reaction.
- Baxter and Whiting have experimentally proved that the least stable, trans-isomer is the major product, and the most stable product is the cis-isomer[1].

Computational Methods



- Above shows mechanism of the ring closure the cis-isomer in the chair formation
- The energy profile of the ring closure is computationally calculated
- The relative energies of the cis-isomer and trans-isomer are calculated as well as the relative energies of the products after the ring closure for both the boat and chair conformations are calculated.
- The computational program that is used for calculations is Turbomole[2].

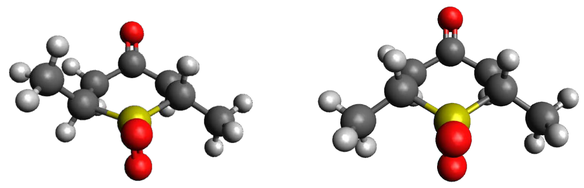
Computational Details

- Energy Calculations for the cis and trans isomers of substituted cyclic sulfones and a ring closure have been successfully performed using computational methods.
- Density Functional Theory (DFT) was used for these computational methods because it has a good balance between efficiency and accuracy.
- The basis set and functional that are used in of the computational calculations are def2-TZVP and PBE0, which are well known to provide accurate energies and structural parameters.
- Internal Reaction Coordinate methods were used to optimize reaction pathways connecting reactants and products.

Results

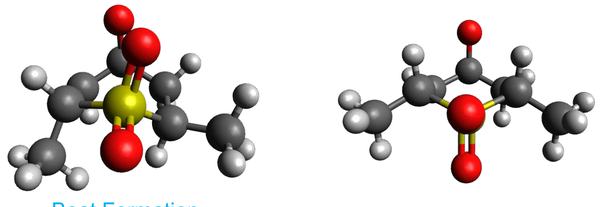
Relative Energies

Energies of the Cyclic Sulfones	
	Relative Energy
Boat Formation	1.9
Chair Formation	
Trans Final Product	5.5
Cis Final Product	



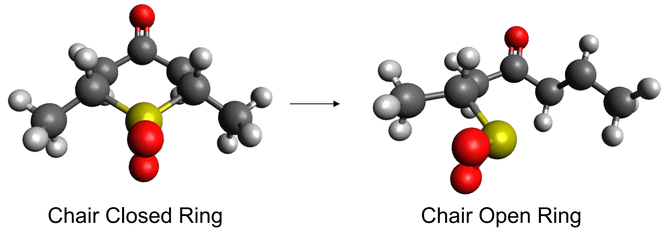
Trans Final Product | Cis Final Product

The relative energy of the final product for both cis and trans conformations is 5.5 kcal/mol. The cis-isomer above is thermodynamically more stable than the trans-isomer.

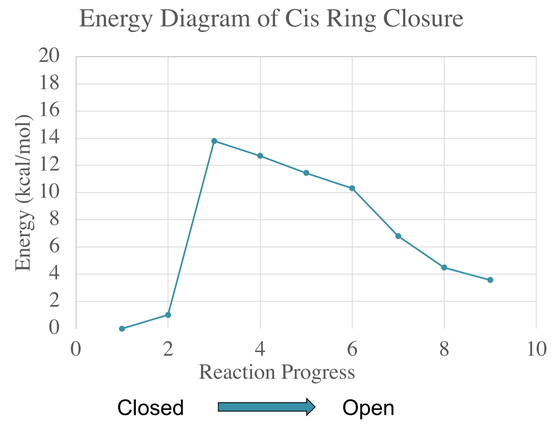


Boat Formation | Chair Formation

The relative energy of the chair and boat conformations after the ring closure and before the final protonation is 1.9 kcal/mol The boat formation above is thermodynamically more stable than the boat formation.



Chair Closed Ring | Chair Open Ring



Conclusions

- So far, It is confirmed that the trans-isomer is less stable than the cis-isomer.
- The trans isomer is the major product
- The energy difference is very small between the two isomers.
- The boat intermediate and the final cis product are more thermodynamically stable than the chair intermediate and the final trans isomer which is in line with Baxter and Whiting's reasoning.
- There is a modest energy barrier for ring opening (~20 kcal/mol)

Future Directions

- Calculate energy profiles of the boat formation ring closure and the profile between the boat and the chair structures before ring closure
- Perform higher level energy calculations to exclude basis set incompleteness error.
- Include solvent effects.
- Perform free energy calculations to include finite temperature effects and zero-point vibrational energies.
- Run conformational searches using molecular dynamics to sample conformational space.

Acknowledgments

- Thanks to Dr.Bebbington for providing useful information

Literature Cited

(1) Baxter, C. and D. A. Whiting. "Stereochemistry and structure in the tetrahydro-1-thio-4-pyrone and tetrahydro-4-pyrone series." *Journal of The Chemical Society C: Organic*(1968): 1174-1178.
(2) "Program Package for Electronic Structure Calculations." *TURBOMOLE*, www.turbomole.org/.