Experimental and Theoretical Investigation of Regioselectivity for a Series of Ketoimines with Nuclear Magnetic Resonance Spectroscopy and Density Functional Theory

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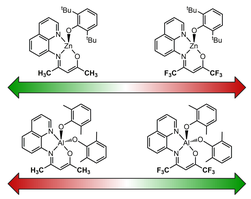
PEPPERDINE UNIVERSITY

Biodegradable Plastics & Synthesis

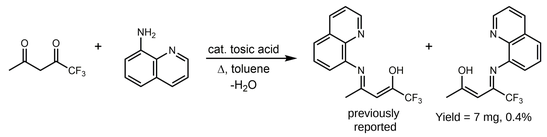
- Seeking to synthesize polymers used in the manufacturing of biodegradable plastics
- Want to synthesize efficient complexes as initiators for polymerization
- Ring-opening polymerization occurs via a coordination-insertion mechanism that is often mediated by inorganic complexes

Ring-opening polymerization (ROP) efficiency of initiating complexes for lactide and ε-caprolactone varies with the electronic properties of supporting ligand and for the metal center.

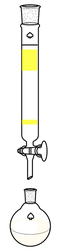


Rezayee, N. M.; Gerling, K. A.; Rheingold, A. L.; Fritsch, J. M. *Dalton Trans.* **2013**, *42*, 5573.
As yet unpublished results.

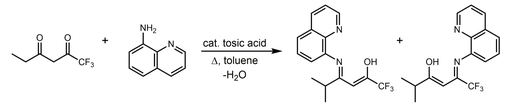
Synthesis of Additional Regioisomer

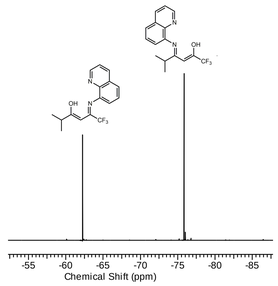


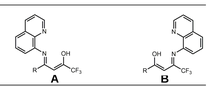
Details
- Dissolved in toluene
- Catalytic tosic acid
- Reaction time extended from 3 h to 18 h
- Isolated with column chromatography (SiO_2 , gradient 8:1 Hex : EtOAc to 3:1 Hex : EtOAc 3% Et_3N)



^{19}F NMR of Reaction Mixtures



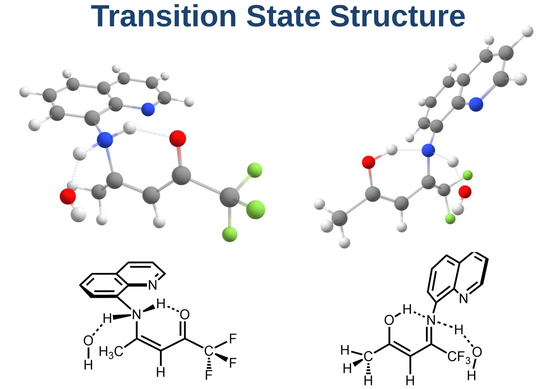




L	A : B Experimental isomer ratio[a]
Me	97(26) : 1
Et	29(2) : 1
^{i}Pr	0.77(6) : 1
^{t}Bu	ND
Ph	0.86(0.2) : 1

[a]Experimental isomeric ratios determined from crude reaction mixture aliquots and ratios of integrals from ^{19}F NMR.

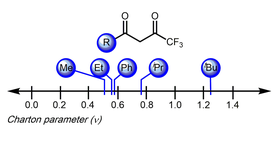
Transition State Structure



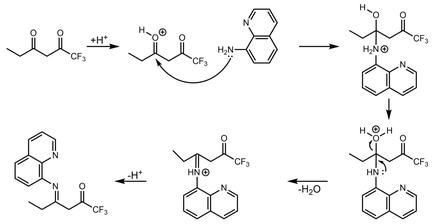
- All transition states had one imaginary frequency corresponding to the stretching of the hydrogen-nitrogen bond towards the water molecule

Varying Electronic Properties

Initiator's ketoiminate supporting ligands prepared by Schiff base condensation of 8-aminoquinoline and 1,3-diketones with varying electronic properties and Charton parameter.



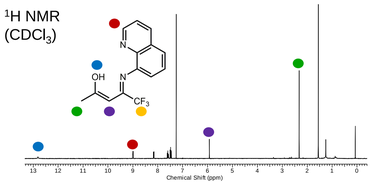
Schiff base condensation mechanism – nucleophilic attack at different carbonyl carbons yields regioisomer ketoimines

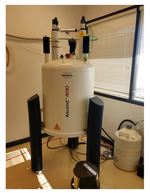


Sigman, M.S., Miller, J.J., *J. Org. Chem.*, **2009**, 74, 7633-7643.

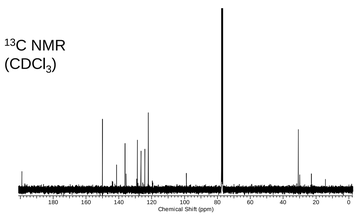
NMR Characterization

^{1}H NMR ($CDCl_3$)

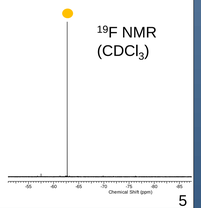




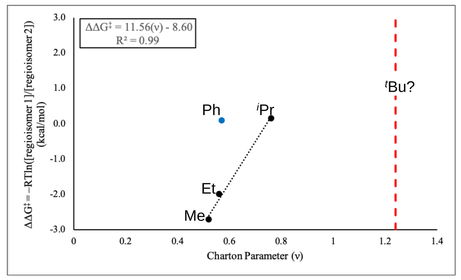
^{13}C NMR ($CDCl_3$)



^{19}F NMR ($CDCl_3$)

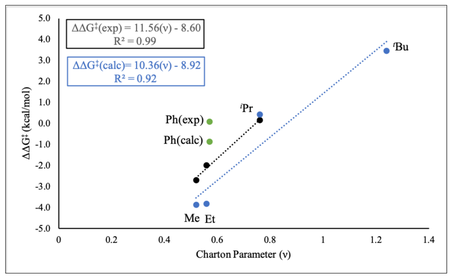


Linear Free Energy Relationship



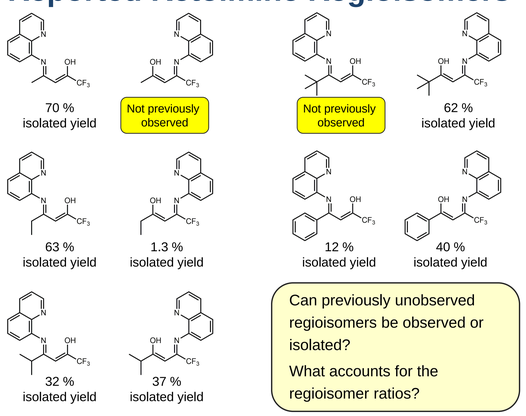
- Correlation between Charton parameters and experimental regioisomeric ratios observed.
- Computational methods pursued to determine energetics for unobserved ^{t}Bu regioisomer

Comparison of Experimental and Theoretical results



- Calculated LFER consistent with experimentally observed ratios.
- Sterically encumbered ^{t}Bu isomer calculated to be < 3 kcal/mol endergonic, consistent with lack of observation experimentally.

Reported Ketoimine Regioisomers



70 % isolated yield

Not previously observed

Not previously observed

62 % isolated yield

63 % isolated yield

1.3 % isolated yield

12 % isolated yield

40 % isolated yield

32 % isolated yield

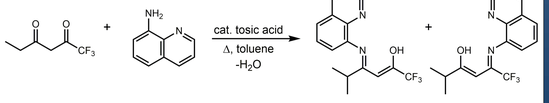
37 % isolated yield

Can previously unobserved regioisomers be observed or isolated?

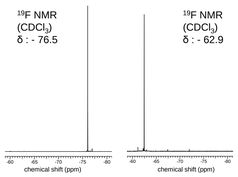
What accounts for the regioisomer ratios?

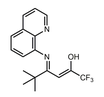
Rezayee, N. M.; Gerling, K. A.; Rheingold, A. L.; Fritsch, J. M. *Dalton Trans.* **2013**, *42*, 5573.
Schmitz, L.A., McCollum, A.M., Rheingold, A.L. Green, D.B., Fritsch, J.M., *Polyhedron*, **2018**, 94.

Syntheses Revisited – ^{19}F NMR



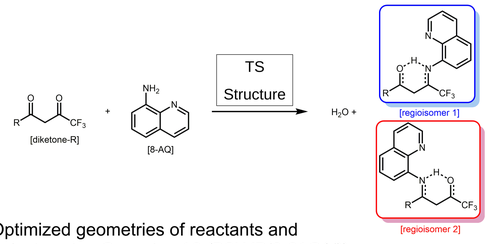
All ketoimine syntheses were repeated and aliquots were drawn, solvent removed in *vacuo*, and analyzed with ^{19}F NMR. Integration of the CF_3 resonances corresponding to the two regioisomer positions were collected.





could neither be isolated nor observed with ~11 x reaction time relative to normal synthesis

DFT Calculations Protocol

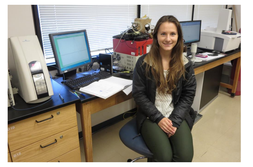


- Optimized geometries of reactants and products using Gaussian 16 (B3LYP/6-31G(d))
- Reactant structures optimized in the same space used to calculate probable transition state structures using QST3 calculations
- Calculated $\Delta G^{\ddagger}$ calculated by the equation:

$$\Delta G^{\ddagger}_{calc} = G_{calc}(\text{TS Structure}) - G_{calc}([\text{diketone–R}] + [\text{8-AQ}])$$

Acknowledgements

Daphne Green
David Green



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