Exploration of the Synthesis of 1-Methyl-4-Silatranone: A Hyperstable Lactam and an Unprecedented Silatrane

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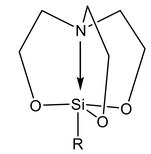


Abstract

Silatranes are a unique group of tricyclic molecules with a nitrogen to silicon transannular dative bond. Silatranes have been studied for over 50 years with special attention to how the dative bond is influenced by substituents on the silicon atom, and have demonstrated potential in diverse fields ranging from medicine to polymer science. Until now, no research has been conducted with regard to influencing the dative bond via modification of the nitrogen interaction.

This project involves the ongoing synthesis of 1-methyl-4-silatranone and preliminary computational analysis of the transannular bond within the silatranone. Completed precursors in the synthetic pathway include 2,2-dimethyl-5-oxo-1,3-dioxolane (glycolic acid acetonide) with a yield of 43.5 % and trace amounts of n-glycolyl-diethanolamine, which is synthesized from the glycolic acid acetonide and diethanolamine.

Computational analysis of the transannular bond in the silatranone predicted a bond length of 2.965 Å in the gaseous phase relative to a calculated bond length of 2.60 Å for 1-methylsilatrane (experimental in gaseous phase is 2.45 Å). Preliminary data indicates that the nitrogen lone pair is shared with the carbonyl rather than the silicon, negating the transannular bond in favor of a hyperstable lactam structure.

Introduction

Silatranes are a fascinating group of molecules due to their tricyclic structure and transannular dative bond. The dative bond is influenced by R-group substituents, as well as any substitutions on the ring components themselves. Research up to this point covers a vast number of combinations of substituents, however it has been limited to interactions through the silicon atom.[1,2] It is not known what would happen if direct competition for the nitrogen lone pair were introduced into the structure, such as a carbonyl adjacent to the nitrogen. There are two possible structures: one with the silicon retaining the nitrogen's lone pair and thus the silatrane structure, or one with the lone pair interacting with the carbonyl to form a structure akin to a bridgehead lactam (figure **1**). The bridgehead lactam structure is predicted to possess 'hyperstability', similar to bridgehead.[3,4] Tentative conclusions can be drawn from computational analysis of the theoretical compound, a silatranone, while completion of a synthetic route with subsequent analysis will provide more concrete proof.

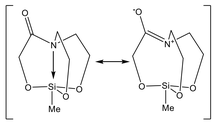


Figure 1: The possible silatrane-like structure on the left compared to the 'hyperstable' bridgehead lactam structure on the right

Silatranes were initially discovered in 1961 by Frye et al.[5], with extensive work conducted since then by Voronkov et al.[1,6], who has published a large volume of research on silatranes over the years, testing their physical properties and developing new synthetic routes. In addition to being excellent subjects for ^{1}H NMR, ^{13}C NMR, X-ray crystallography, and computational analysis, silatranes are also relevant in commercial and biological applications. Silatranes range from stimulating hair growth and collagen repair, to possessing anticancer/tumor/bacterial/fungal activity. How effective a silatrane is in each of these situations is determined by its substituents. For example, when substituted with a phenyl group, silatrane becomes a potent neurotoxin with twice the toxicity of strychnine.[6]

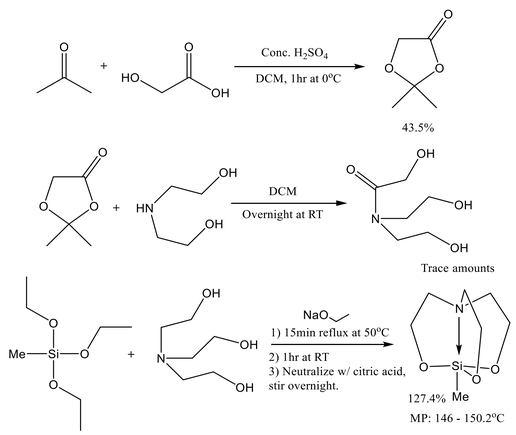
Computational

Bond lengths and relative energies were calculated using density functional theory with the B3LYP functional and Pople 6-311+G** basis set. Transannular bond lengths for the 1-methyl-4-silatranone with different ring conformations were calculated, along with the bond length for 1-methylsilatrane as a comparison. Relative energies between the different ring conformations were also calculated, showing progression of the silatranone undergoing a complete ring flip to its enantiomer. Calculations were conducted on a single-molecule model, meaning that any theoretical values obtained are in a gaseous state. Reported experimental bond lengths and angles were obtained by electron diffraction. In the gaseous state, transannular bond lengths are longer. The bond in the solid state is shorter as a result of thermal effects and some packing; experimental values are obtained via X-ray crystallography.

Experimental data reveals that 1-methylsilatrane has a dative bond length in the gaseous state of 2.45 Å and a solid state length of 2.173 Å, while a calculated gaseous state using the above method is 2.60 Å. Such bond stretching in 1-methylsilatrane can be attributed to the higher temperatures in the gas phase, where dative bonding is essentially non-existent.10 When substituted with an electron-withdrawing group such as fluorine, experimental values for the dative bond are 2.324 Å in the gaseous state and 2.042 Å in the solid state, indicating tightening of the bond, even with some back-donation from the fluorine atom.

1-methyl-4-silatranone has a calculated, gaseous state dative bond length of 2.965 Å, which is the same for its enantiomer after a complete ring flip. While the silatranone is projected to be quite stable, such large values for the dative bond indicate that such an interaction between the nitrogen and silicon is unlikely, and that the lone pair is probably donated to the carbonyl. The conformational ring flip has low calculated barriers, only requiring up to 3.05 kcal/mol.

Synthetic Pathway



^{1}H and ^{13}C NMR for 1-Methylsilatrane

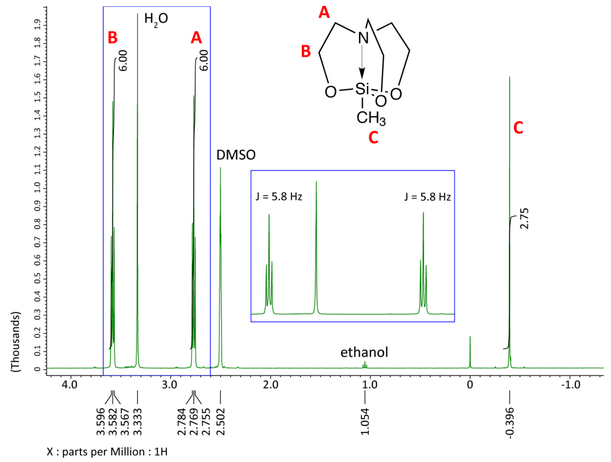


Figure 2: ^{1}H NMR of synthesized 1-methylsilatrane

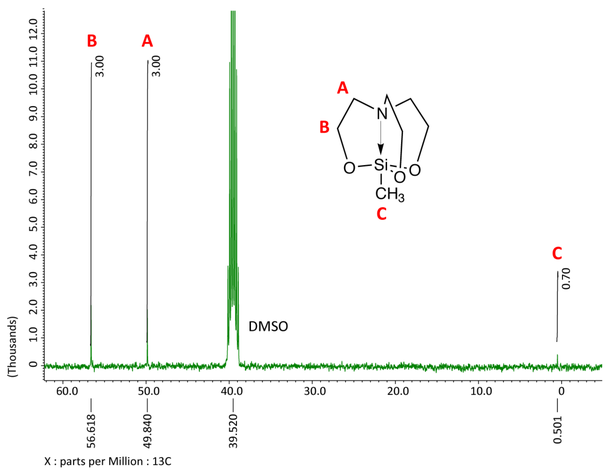


Figure 3: ^{13}C NMR of synthesized 1-methylsilatrane

^{1}H and ^{13}C NMR for Silatranone Precursors

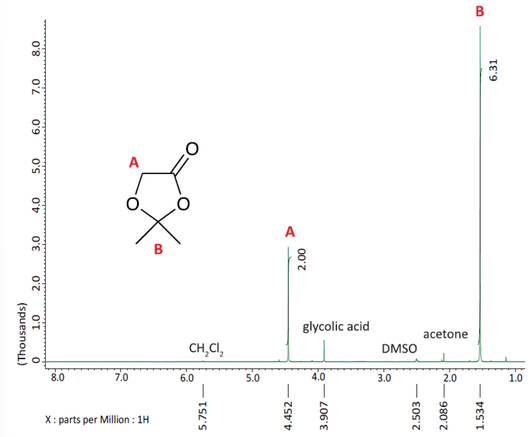


Figure 4: ^{1}H NMR of synthesized glycolic acid acetonide

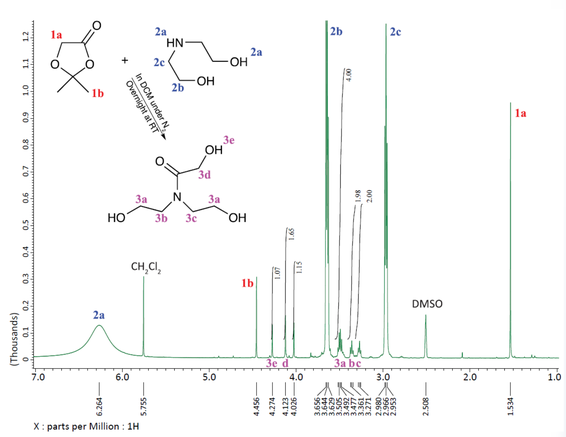
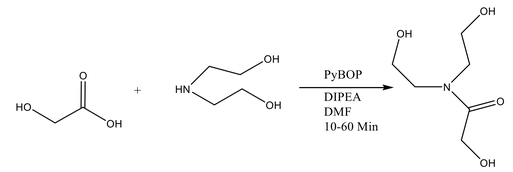


Figure 5: ^{1}H NMR of synthesized *N*-glycolyl-diethanolamine in trace amounts with the presence of starting materials.

Future Work

- In depth analysis of the final product through ^{1}H NMR, ^{13}C NMR, IR, and X-ray crystallography.
- Continue computational analysis of siltranone and silatrane derivatives using Density Functional Theory (DFT), with particular attention to how substituents influence the dative bond.
- Devise a cleaner, easier, and higher yielding synthetic pathway of N-glycolyl-diethanol amine using coupling of secondary amine as proposed below
  - Utilizing a stronger activating agent than DCC, PyBOP, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, or regular BOP, (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate), one is able to couple secondary amines to carboxylic acids.
  - Using BOP creates a carcinogenic byproduct, therefore, it would be more beneficial to use PyBOP as it does not have this byproduct.



- Using this synthesis should procure higher yields in a shorter amount of time for the desired product as the synthesis of pure *N*-glycolyl-diethanolamine has been halting the process of the final reaction in order to attain 1-methylsilatranone.

Conclusion

Preliminary computational analysis indicates formation of the 3.3.3 bridgehead lactam, based on a calculated bond length of 2.965 Å in the silatranone relative to a calculated length of 2.60 Å in 1-methylsilatrane. In the synthetic pathway, *N*-glycolyl-diethanolamine has been synthesized in trace amounts however further work is required to improve the reaction as well as purification of the crude product. A model synthesis of 1-methylsilatrane was proven successful and will be used in the final step for synthesis of 1-methyl-4-silatranone.

Acknowledgements

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