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Thermochemical and structural analysis of tautomers of sulfur and selenium modified RNA nucleobases

Megan Joy[1], Alex Brown[1], Maria Rossano-Tapia[1], Shyam Parshotam[1], Arturo Mora Gomez[1]

[1]Department of Chemistry, University of Alberta

Abstract

Nucleobases (adenine, cytosine, guanine, and uracil), the four molecules that forms RNA, have been found to be useful in probing in the human body when modified because they can emit light. Non-modified nucleobases do not exhibit emissive properties and cannot be used as probes. Some of the modifications include the substitution of nitrogen atoms with sulfur and selenium, and the resulting modified nucleobases give place to the so-called tz- and ts- RNA alphabets, respectively. Therefore, the aim of this project was to provide insights about the viability, from a computational perspective, of using the modified nucleobases as probes, evaluating the differences in thermochemical, structural and emissive properties of the modified nucleobases with respect to the non-modified ones. Nucleobases can coexist with other modified nucleobases or tautomers, molecules that differ due to the change in position of hydrogen atoms in a molecule's structure and as a result have different physical and chemical properties. The thermochemical properties evaluation mainly consisted in the computation of the relative Gibbs Free Energy (G), which is related to the fraction F, an index of the relative population among tautomers. This was done using Gaussian 09 software by performing geometry analysis and frequency computations on each one of the tautomers. By comparing the equilibrium fractions, it was determined that in both cases, tz- and ts- guanine and cytosine exist principally in the form of one of their tautomers (Cytosine 2 and Guanine 2) as in the case of the non-modified cases. After confirming which tz- and ts- tautomers were the ones with the largest probable population, infrared (IR) and ultraviolet-visible (UV-vis) spectra were obtained. The IR spectra of selenium and sulfur tautomers of guanine and cytosine indicated that the tautomers had peaks at similar frequencies with respect to each other, however, the intensities varied, implying slight structural changes between the tautomers. On the other hand, the UV-vis spectra showed a change in peak positions between the tautomers with sulfur and selenium, suggesting that the change between sulfur and selenium has an effect on the spectra by shifting the peaks from the original molecules' λmax values. Their relative population fractions show that only the canonical forms of the modified nucleobases exist in a larger extent than the rest of their tautomer forms. In addition, the features in their UV-vis and IR spectra allow these tautomers to be differentiated from each other.

Key words:
Nucleobases, RNA, sulfur, selenium, tautomers, emissive, computations, structural analysis

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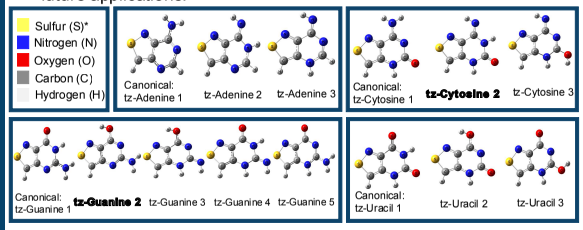
The Thermochemical and Structural Analysis of Tautomers of Sulfur and Selenium Modified RNA Nucleobases

Megan Joy, Maria Rossano-Tapia <rossanot@ualberta.ca>, Arturo Gomez <moragome@ualberta.ca>, Shyam Parshotam <parshota@ualberta.ca>, Dr. Alex Brown <alex.brown@ualberta.ca>
Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2, Canada

Introduction

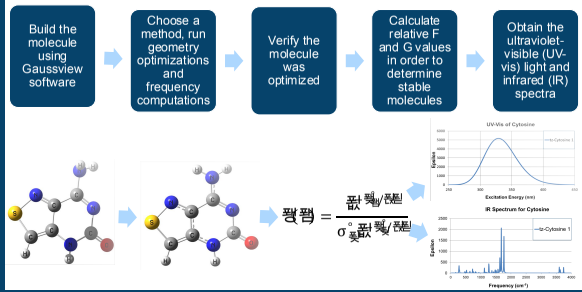
- Nucleobases are found in all living species and are the building blocks of RNA and DNA.[1]
- The emissive properties of modified nucleobases have been discovered to be useful for probing in comparison to their non-emissive canonical structures.[2,3]
- The purpose of this research is to analyze the previously studied nucleobases containing sulfur (tz- molecules) and nucleobases containing selenium (ts- molecules).[2] In doing so, the tautomers with the most stable and beneficial properties can be used in future applications.



*Sulfur atoms were replaced with selenium atoms for the ts- set of molecules that were analyzed

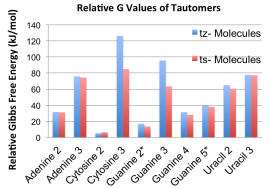
Methods

- The analysis of these molecules was done using Gaussian 09 computational chemistry software.[4]
- Geometry optimizations and frequency computations were performed using the semi-empirical PM6 method and was followed by the density functional theory (DFT) method with B3LYP/6-31++G(d,p) level of theory.[5] Time-dependent density functional theory (TD-DFT) computations were done with B3LYP/6-31+G(d,p) level of theory.[6]
- The methodology followed for this research:



Results and Discussion

Which Molecules Are The Most Stable?



* The molecule did not fully converge while undergoing computations

Figure 1. The relative G values of nucleobase tautomers. The relative G value is the difference of Gibbs Free Energy between the original molecule and the tautomer.

Table 1. The equilibrium fractions of tautomers found by using the relative G values. Each number represents their stability and presence in an equilibrium with other forms of the nucleobase (the larger the value, the more stable).

Tautomer	Equilibrium Fraction for tz-Molecules	Equilibrium Fraction for ts- Molecules
Adenine 2	3.11×10^{-6}	3.54×10^{-6}
Adenine 3	5.42×10^{-14}	9.71×10^{-14}
Cytosine 2	**0.121**	**0.0753**
Cytosine 3	7.09×10^{-23}	1.29×10^{-15}
Guanine 2	$\mathbf{1.12\times10^{-3}}$	$\mathbf{4.55\times10^{-3}}$
Guanine 3	1.78×10^{-17}	8.01×10^{-12}
Guanine 4	3.33×10^{-6}	1.27×10^{-5}
Guanine 5	1.18×10^{-7}	2.20×10^{-7}
Uracil 2	4.18×10^{-12}	2.51×10^{-11}
Uracil 3	2.47×10^{-14}	2.98×10^{-14}

How Can These Molecules Be Detected Experimentally?

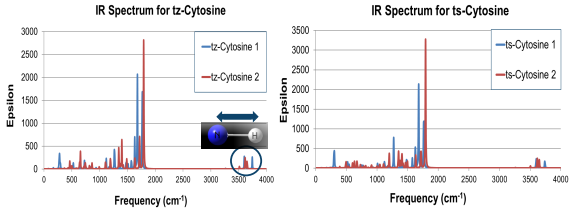


Figure 2. The IR spectra for Cytosine 1 and its tautomer Cytosine 2 with sulfur and selenium, respectively. Each peak represents the vibration of a specific bond in the molecule, for example, the peak found in the N-H bond range between 3500-4000cm^{-1}. For both graphs, tautomer peaks have a greater intensity and peaks are shifted to the right compared to the canonical molecules.

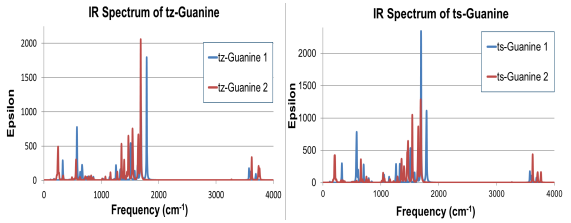


Figure 3. The IR spectra for Guanine 1 and 2 with sulfur and selenium. Tz-Guanine 2 has a greater intensity compared to the ts-Guanine 2 molecule; however, the results are similar in that the peaks for the ts- and tz- molecules are occurring at roughly the same frequencies.

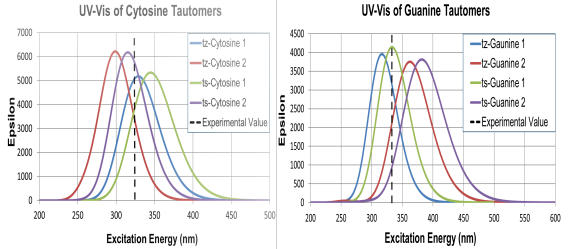


Figure 4. The UV-vis spectrum for Cytosine 1 and 2 with sulfur and selenium, and Guanine 1 and 2 with sulfur and selenium. Peaks represent the molecule's electronic excitation after absorbing light in the UV-vis region. The vertical dotted lines represent the experimental λ max values for tz-Cytosine 1 and tz-Guanine 1 molecules for comparison.[2]

Conclusions

- The four most stable tautomers are tz-Cytosine 2, ts-Cytosine 2, tz-Guanine 2 and ts-Guanine 2, which can be seen through the relatively high equilibrium fractions and low relative G values.
- The cytosine tautomer's stability can be attributed to the double bonded oxygen atom, but the oxygen atom has the opposite effect on the guanine tautomers.
- The adenine and uracil tautomers were not looked at due to the high relative G values and low equilibrium fractions, suggesting instability at equilibrium.
- Based on the UV-vis and IR spectra, these four tautomers should be detected separately experimentally from their canonical forms due to their shifted peak positions. This difference can guide experimentalists performing experiments with these molecules.

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