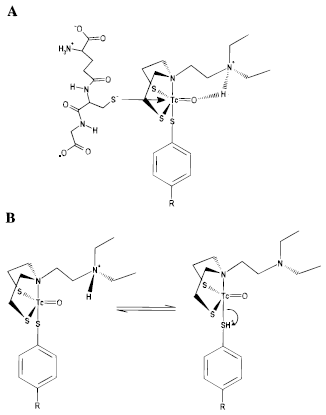
***A Computational Investigation of a Proposed Reaction Mechanism of Brain Retention***

**Abstract:** I propose to perform an extensive computational analysis on the two proposed reaction mechanisms put forth in [1] by Nock et al, which are possible explanations as to why [99mTc](SNS/S) mixed ligand complexes with *N*-diethylaminoethyl ligands are more reactive with GSH as opposed to complexes with *N*-ethyl ligands. Using this data, the two proposed mechanisms will be compared with respect to their thermodynamic data—particularly their entropies, enthalpies, internal energies, and Gibbs free energies—to determine which of the two proposed mechanisms is more likely with respect to thermodynamics.

**Motivation:** The [99mTc](SNS/S) mixed ligand complexes studied by Nock et al. in [1] are associated with intracerebral glutathione (GSH), and were concluded to have potential as 99mTc agents able to assess intracerebral GSH levels in vivo. There are a number of prevalent brain disorders involved with changes in intracerebral GSH content, such as Alzheimer’s and Parkinson’s diseases, as well as brain injury caused by ischemia, inflammation, and aging. There are previous studies which have proposed [99mTc](HM-PAO) as a possible imaging agent for GSH localization in the human brain [3]. However, as described by Nock et al., the SNS/S complexes are a more viable 99mTc agent due to the fact that their mechanism is directly dependent on GSH concentration. Whereas in the case of HM-PAO, the mechanism is a combined effect of a parallel “auto decomposition” process. With my proposed research plan, I hope to provide further information about the SNS/S complexes so as to contribute to a deeper understanding of these complexes with respect to their thermodynamic properties, as well as to determine the more likely reaction mechanism for *N*-diethylaminoethyl ligand complexes with respect to their interaction with GSH.

**Figure 1.** Two mechanisms proposed by Nock et al. for the reactivity of N-diethylaminoethyl [1].

**Previous Findings:** In their study, Nock et al. concluded that the brain-retention mechanism of [99mTc](SNS/S) complexes is GSH-mediated and directly correlated with GSH concentration, and therefore that these SNS/S complexes could potentially be used in the diagnosis of GSH-related brain diseases. In their study, two series of SNS/S complexes each carrying the *N*-diethylaminoethyl or *N*-ethyl ligand were tested for their relative resistance against nucleophilic attack of GSH. It was concluded that the *N*-diethylaminoethyl complexes were more reactive against GSH as compared to the *N*-ethyl complexes.

**Research Proposal:** This research plans to expand upon the conclusions put forward in [1] by Nock et al., particularly with respect to the two proposed mechanisms for the brain retention mechanism of [99mTc](SNS/S) complexes, mediated by GSH, shown in Figure 1. I plan to build upon their conclusions to provide a more in-depth understanding of the SNS/S complexes with respect to their thermodynamic properties, as well as to produce computational data which can help shed light on which of their two proposed mechanisms are more likely.

More specifically, I have three main goals. Firstly, it was discussed that the *N*-diethylaminoethyl complexes were more reactive with GSH as compared to the *N*-ethyl complexes. I plan to use Gaussian [2] to construct a series of six SNS/S mixed ligand complexes, in which 3 complexes will have the R1 group as *N*-diethylaminoethyl and in which the R2 groups are NH2, H, and NO2, respectively, and 3 complexes will have the R1 group as *N*-ethyl and in which the R2 groups are NH2, H, and NO2, respectively. Having constructed these six mixed ligand complexes, I will then optimize each of the six structures. Having done so, I will calculate their thermodynamic data, which will be used to compare the *N*-diethylaminoethyl and *N*-ethyl ligands. For each of the six compounds, I will also determine the distribution of charge and spin in each of the different species. Secondly, the paper supplies the reaction scheme for the reversible nucleophilic attack of GSH on the metal center of the mixed ligand complexes. I plan to use Gaussian [2] to calculate data for the thermodynamic properties of each of the compounds involved with this nucleophilic attack mechanism. I also plan to calculate the Gibbs free energy, internal energy, enthalpy, and entropy for this overall reaction. This will allow for further understanding of the interaction between GSH and the SNS/S complexes. Thirdly, Nock et al. proposed two possible mechanisms which could explain the increased reactivity of the *N*-diethylaminoethyl complexes against GSH. I plan to use Gaussian [2] to calculate thermodynamic data for each of the two proposed mechanisms, and then compare the results for the two possible mechanisms to determine which is more likely with respect to thermodynamics.

**Intellectual Merit:** The computed thermodynamic data which will result from my research may prove useful for further work related to 99mTc complexes. Currently, the search for the ideal 99mTc-based brain agent—widely used in clinics as a radiopharmaceutical when diagnosing various cerebrovascular and neurological disorders—is ongoing, according to Nock et al. Therefore, contributing this data to the scientific community may help provide further insight into current knowledge on 99mTc complexes.

**Broader Impact:** A more accurate and in-depth understanding of the interactions between the [99mTc](SNS/S) complexes and glutathione has direct implications in the ability to screen for and diagnose prevalent pathologies such as Alzheimer’s and Parkinson’s diseases. If my research is successful, there is potential for screening and diagnosis of these brain diseases to vastly improve via a deeper understanding of the involved mechanisms, thereby benefiting society.

[1] *J. Med. Chem*. 1999, 42, 6, 1066-1075.

[2] Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

[3] Sharp, P. F.; Smith, F. W.; Gemmell, H. G.; et al. Technetium-99m HM-PAO stereoisomers as potential agents for imaging regional cerebral blood flow. *J. Nucl. Med*. 1986, 27, 171-177.