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Re: Doctoral Thesis: Zdeněk Futera

I have examined Mr. Futera's doctoral thesis and come to the following conclusions.

Mr. Futera reports quantum mechanical and hybrid quantum mechanical/molecular mechanics (QM/MM) studies on the mode of anti-cancer action of Ru(II) "piano-stool" complexes, their interaction with DNA and their reactivity. This is a formidable computational task because of the size of the biological target system and the relative complexity of the reactions and interactions to be investigated. The inherent flexibility of the biological system means that simple geometry optimization cannot be used to characterize stationary points in reactions, but rather that the dynamics of the system must be taken into account. The combination of the need to treat both a transition-metal complex and a flexible biological system correctly represents a daunting computational task that is worthy of a doctoral thesis.

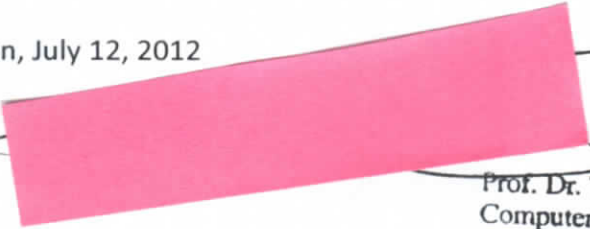
Because the total system is too large to be treated by a reliable quantum mechanical technique, faster methods must be used in order to achieve the necessary conformational sampling demanded by the flexibility of the system. However, no reliable but fast methods exist for Ru(II) complexes, so that at least this part of the calculation must be performed with a reliable but expensive quantum mechanical method. The solution is to treat the transition-metal center quantum mechanically and the remainder of the system with a force field in hybrid QM/MM method. Mr. Futera wrote a series of scripts and programs in order to be able to perform such calculations efficiently by combining existing quantum and classical mechanical programs.

The thesis begins with a discussion of transition-metal compounds in cancer therapy before giving an understandable and accurate overview of the calculational techniques used. This section demonstrates that Mr. Futera both understands and appreciates the details of the techniques that he has used and that he is well able to judge which technique is suitable for which problem.

In the second half of his thesis, Mr. Futera reports the results of his studies on the Ru(II) piano-stool systems. This work has been performed at a most competent level and with a thorough appreciation of the possible pitfalls of the calculational methods for the problem in hand. Where possible, higher level calculations were performed in order to validate the results.

Mr. Futera's thesis demonstrates convincingly that he has a firm grip on the theory and practice of computational chemistry and biology and that he is able to perform creative scientific work at a high level.

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