Can noncovalent interactions be visualized and interpreted using the random phase approximation?

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Introduction

Natural products have served as models for designing new anticancer drugs over the past several decades.[1,2] One example is the chlorolissoclimide (CL) extracted from the ascidian *Lissoclinum voeltzkowi* which inhibits cell growth by binding to eukaryotic ribosomes and preventing translation.[3] The X-ray co-crystal structure of CL with the eukaryotic 80S ribosome revealed a novel halogen–π interaction between the ligand's alkyl chloride and two guanine nucleotides.[4,5] However, the specificity of the halogen–π interactions is not well understood. In this project, I will address the problem by developing a computational tool based on electronic structure theory to characterize and visualize noncovalent interactions (NIs) that can then be used to guide the design and synthesis of lissoclimide analogues for new cancer therapeutics.

To achieve the project's goal, the correct computational and theoretical understanding of dispersion interactions is key to designing new therapeutics. Dispersion interactions are viewed as long-range electronic interactions that are non-trivial to compute and difficult to characterize. In a recent publication, we demonstrated that nonperturbative methods such as the random phase approximation (RPA) provides the correct description of dispersion interactions compared to the many-body perturbation theory (MBPT) for NIs.[6] RPA is an unprecedented theory that achieves this accuracy without any additional empirical parameters while remaining computationally efficient. Based on this study, I propose using RPA to develop a tool for characterizing dispersion interactions and verifying the tool with a simplified model of the intermolecular interactions between the CL and eukaryotic 80S ribosome, see Fig. 1.

Research Plan

The halogen-π interactions between the CL and ribosome were studied based on a simplified model by Könst *et al.*[5] I have performed preliminary work by improving upon this model and varied the halogen moiety (X = F, Cl, Br, I, CH_3), see Fig. 1, that showed binding energies increasing going down the halogen group. In addition, the methylissoclimide surprisingly yielded a binding energy within 2 kcal/mol compared to iodolissoclimide. Dispersion interactions are suspected but, these remain to be intuitively understood. Hence, I will be spending time with Prof. Filipp Furche attempting to capture and visualize the spontaneously induced electronic attractions through analyzing the corresponding eigenvectors of the RPA correlation energy. Lastly, I will work with Prof. Christopher Vanderwal to refine and confirm the computational tool through the synthesis of the substituted lissoclimide along with testing the drug's potency through *in vitro* studies.

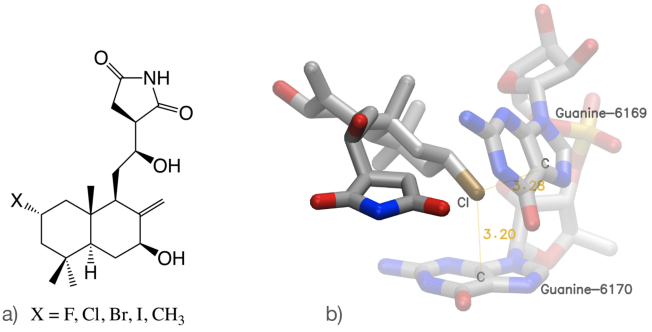

Figure 1: a) A series of substituted lissoclimides of different halogens. b) Geometry optimized model of CL and guanine nucleotides using the hybrid density functional TPSSh-D3.[7,8] Bond lengths are in Angstroms. Hydrogens were removed for clarity. Color codes for atoms are Cl = brown, N = blue, C = gray, O = red, and P = orange.

Contribution to Doctoral Dissertation

For my doctoral studies, I have envisioned my dissertation to be focused on developing state-of-the-art approaches that accurately describe NIs. We have concluded from our recent landmark publication that RPA with its superior accuracy for NIs may safely replace MBPT for predictions of NIs in most systems of chemical interest.[6] With this research project, I will be able to apply diverse skills from organic synthesis and theoretical chemistry to develop RPA based methods that interpret NIs relevant for drug design.

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