

Theoretical and Computational Chemistry Group @ UWA

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Assist. Prof. Karton established the group of theoretical and computational chemistry at the School of Chemistry and Biochemistry in late 2012, after moving from the University of Sydney where he held a prestigious ARC APD Fellowship. Since completing his PhD at the Weizmann Institute in 2010, Amir has had a distinguished research career. He has published more than 55 articles in prestigious international journals. These articles have been cited well over 1700 times in the scientific literature, and he has played a key role in the development of quantum chemical theory and the application of quantum chemical procedures to problems of structure, mechanism and design.

Theoretical and Computational Chemistry Group

During the past decade, computational chemistry has had an increasingly important impact on almost all branches of chemistry as a powerful approach for solving chemical problems at the molecular level. The increasing computational power provided by supercomputers and the emergence of highly accurate theoretical procedures make contemporary computational chemistry one of the most detailed “microscopes” currently available for examining the atomic and electronic details of molecular processes. In my lab we use supercomputers in conjunction with very accurate theoretical methods to elucidate the reaction paths, kinetics, and the mechanisms in salient organic, organometallic and enzymatic systems.

PROJECTS

1. Computational Antioxidant Design

Oxidative damage to DNA and proteins is a major cause of many chronic inflammatory diseases including conditions such as cancer, arthritis and cardiovascular disease. In recent work, we elucidated the molecular mechanism by which the potent endogenous antioxidant carnosine operates (Fig. 1). We showed that a unique structural relationship between three adjacent functional groups (imidazole, carboxylic acid and terminal amine) enables carnosine to work via a novel two-step mechanism. Initial chlorination occurs at the imidazole nitrogen (the kinetically favoured site), followed by an intramolecular Cl transfer in which the Cl is transferred to the terminal primary amino nitrogen (the thermodynamically favoured site) effectively trapping the chlorine. This bifunctional mechanism is illustrated schematically in Fig 2. Based on this discovery of carnosine’s two-step mechanism, we designed improved bifunctional antioxidants against HOCl-mediated oxidative damage. The bioinspired antioxidant trap the noxious chlorine atom at rates several orders of magnitude faster than carnosine. *This work was featured in the Research Highlights section of Nature Chemistry* and opens the way for further computational design of potent bifunctional antioxidants that selectively target strong HOX oxidising agents. The aim of this Honours project is to provide an innovative basis for the development of new antioxidants to alleviate or circumvent the damage resulting from HOX-induced oxidative stress. The project will decipher the reaction mechanisms by which HOX oxidise biologically important purine bases (e.g. guanine, cytosine,

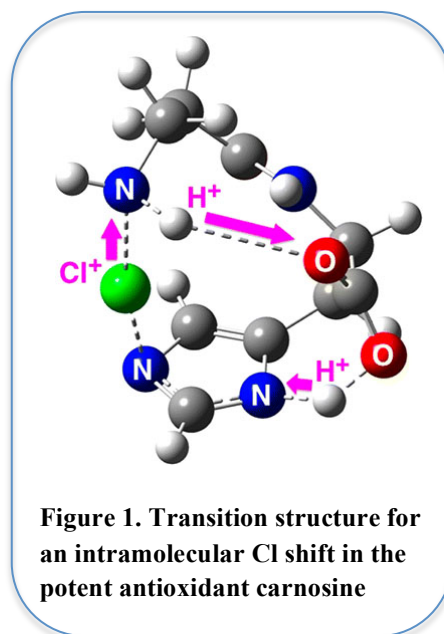


Figure 1. Transition structure for an intramolecular Cl shift in the potent antioxidant carnosine

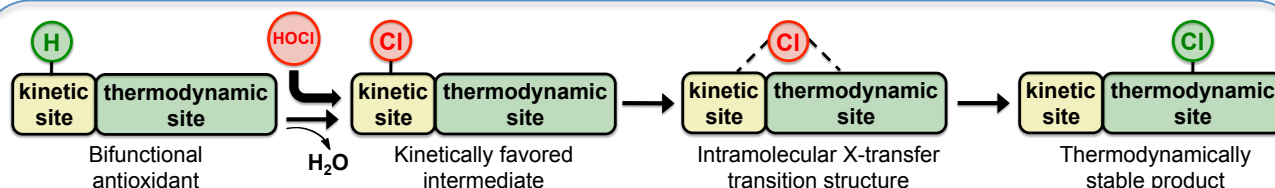


Figure 2. Schematic representation of the reaction mechanism underlying the activity of the antioxidant carnosine

thymine, uracil), and other biomolecules incorporating nitrogen-heterocycle functionalities (e.g. substituted imidazole, pyrazole, diazines, naphthyridine). These biomolecules are ideal candidates to serve as “kinetic traps” in bifunctional antioxidants; e.g. carnosine uses an imidazole ring as the kinetically preferred site (Fig. 2). These heterocycles have multiple N–H sites that are prone to oxidation. The project will address questions such as (i) which sites are kinetically favoured and which are thermodynamically favoured, (ii) what are the rate-determining steps, and (iii) can we control the outcome by changing the reaction conditions (e.g. temperature, solvent, etc.)? These discoveries will allow us to design novel bioinspired antioxidants that specifically target the HOX-mediated oxidative stress occurring in many chronic diseases.

2. Chemistry in Outer Space

A recent study, based on data collected from NASA's Kepler space telescope, shows that roughly 20% of the Sun-like stars in the Milky Way galaxy have an Earth-like planet orbiting around it in the so-called ‘goldilocks’ zone, i.e. at distances from the star that produce the right temperature for surface liquid water. According to this study there are as much as 40 billion such planets that could potentially support life in the Milky Way galaxy alone. This raises the fundamental question (which is also relevant to our Earth): which complex organic molecules can be synthesized in the interstellar medium, and can they be delivered to these planetary systems? (see Fig. 3). This project will elucidate the reaction mechanisms by which prototypical organic molecules are synthesized in space, using composite quantum chemical theories to determine the main mechanistic aspects underlying molecular formation in the gas phase under interstellar conditions. This will involve such issues as locating the (i) preferred chemical routes for the formation of prototypical molecules that have been observed in the interstellar medium (e.g. methanol, formaldehyde, and formamide), (ii) expected products of subsequent reactants (e.g. hydrogenation and oxidation processes), (iii) pathways by which the observed products may react to give more complex organic molecules (e.g. small PAHs and biologically-relevant molecules such as amino acids and carbohydrates), (iv) reaction pathways by which unstable complex species may decompose to give simple products, and (v) the effect of temperature on these processes.

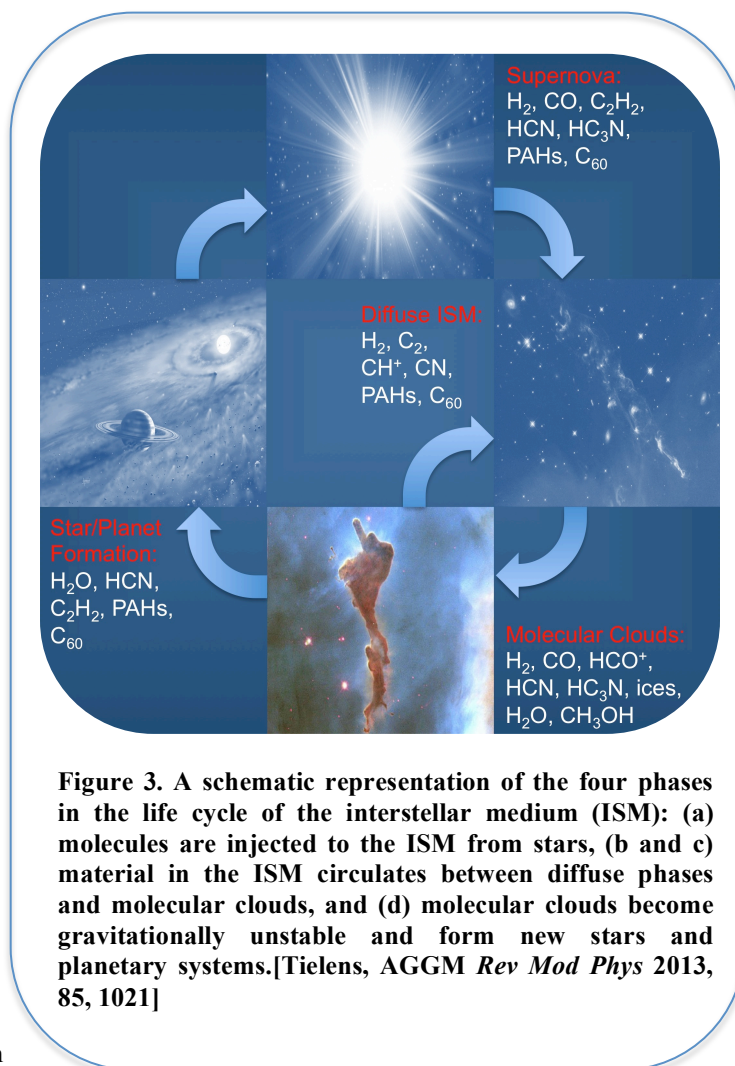


Figure 3. A schematic representation of the four phases in the life cycle of the interstellar medium (ISM): (a) molecules are injected to the ISM from stars, (b and c) material in the ISM circulates between diffuse phases and molecular clouds, and (d) molecular clouds become gravitationally unstable and form new stars and planetary systems.[Tielens, *AGGM Rev Mod Phys* 2013, 85, 1021]

PREREQUISITES

- 1) We are looking for highly motivated students who are interested in the area of theoretical chemistry
- 2) A background in organic and/or biological chemistry is an advantage
- 3) Background in programming (e.g. C, Perl, or Fortran) and a UNIX environment is an advantage