

Sept 3, 2018

External examiner report for the thesis 'Investigations into chalcogen bonding' by Thomas Fellowes, School of Chemistry and Bio21 Institute, the University of Melbourne

The thesis entitled 'Investigations into chalcogen bonding' by Thomas Fellowes describes a substantial and significant contribution to fundamental knowledge in the area of chemistry. The candidate's work has provided insight into a noncovalent interaction of group 16 elements known as chalcogen bonding. Explorations of structure and bonding have been central to the chemistry discipline throughout its existence, and 'unconventional' noncovalent interactions such as chalcogen bonding are at the forefront of the field.

The main techniques employed by the candidate include organic synthesis, crystallography and quantum chemical calculations. It is clear from the document that the candidate has built expertise in both the theory and practice of these techniques. Experimental details and characterization data have been provided in accordance with accepted norms for the discipline, and fully support the conclusions of the thesis work. Three peer-reviewed publications in reputable journals have already arisen from the candidate's research contributions, and another manuscript has been posted to chemRxiv in advance of submission to a journal.

The quality of the writing is generally excellent. I especially appreciated the descriptions of the computational methodologies (Chapter 2), which were impressive in their clarity and in their accessibility to a non-specialist reader. I have a few minor comments related to style/grammar/typographical errors that are provided at the end of this report.

Chapter 1 provides an overview of the chalcogen bonding interaction, introducing the phenomenon, its significance and applications, and current understanding of the nature of the interaction. Chapter 2 introduces the major techniques used, including their practice, interpretation and limitations. Spectroscopic and crystallographic characterization of the chalcogen bonding interactions of organoselenium compounds is a main theme of the thesis, described in Chapters 3, 4 and 7. In chapter 8, attempts at developing a DNA-binding compound incorporating a selenium-based chalcogen bond donor are described. Although the goals of the work were not fully realized, this was an interesting and ambitious line of research that exposed the candidate to new ideas and techniques. Chapters 5 and 6 describe crystallographic and computational evidence for intramolecular chalcogen bonding interactions in nitro-substituted oxime derivatives. These are intriguing results, because chalcogen bonds of second row elements are expected to be weak, and there has been sparse experimental support for their existence. Chapter 9 delineates an approach for adjusting molecular mechanics force fields to account for the the electron density distribution at selenium in the antioxidant ebselen. The results demonstrate that the parameters enable the correct description of geometries and interaction energies for complexes of ebselen. Chapter 10 provides a summary of the key findings and identifies possible directions for future work.

In my view, the thesis clearly meets the criteria for acceptance of a doctoral thesis. The comments and suggestions provided on the following pages should be straightforward to address, and I would be comfortable with the Chair of Examiners checking these revisions. I congratulate the candidate on his contributions to science and his well-written thesis.

Comments/suggestions to consider:

Chapter 1: Reference 26 is a somewhat unconventional choice of representative study regarding halogen bonding interactions of iodoperfluoroalkanes and iodoperfluoroarenes. Earlier work had been carried out by other groups, including Resnati (1998), Hunter (2009) and Taylor (2010).

Chapter 2: When describing previous work on tellurium- and selenium-based heterocycles (e.g., page 52), it might be preferable to mention the corresponding author of this work (Vargas-Baca et al, rather than Ho et al).

Chapter 3, Re: discussion of the nature of chalcogen bonding (pp 52-53): mutual polarization is another phenomenon that is often invoked. This is maybe responsible for some of the debate around this topic, since it occupies a grey area between classical electrostatic (unperturbed molecular electrostatic potentials) and dispersion (induced dipole-induced dipole). It might be worth including this in the discussion along with some references (Huber and co-workers Chem. Commun. 2012, 48, 7708 describes this effect for XB – it may be possible to find others for CB). Chapter 9 alludes to this issue, but it would ideally be introduced at an earlier stage of the thesis.

Chapter 3, Page 61 (and subsequent experimental sections): coupling constants should be reported to the nearest 0.1 Hz, not 0.01 Hz. When stating temperatures, there should be a space between the number and the units (n °C, not n°C). ¹³C NMR chemical shifts should be reported to the nearest 0.1 ppm.

Chapter 4, Page 81: implicit in the Hammett analysis of internuclear distances from crystal structures is the idea that bond distances are linearly proportional to a free energy over the range of complexes examined. Is there a fundamental basis for this idea? It seems to me that such a linear relationship should have limits at both ‘ends’ (very strong interaction or vanishingly weak one). This issue merits further discussion in the thesis.

Chapter 4, Page 103: analysis of solution-phase binding data without assuming constant [base] involves straightforward fitting to a quadratic equation (it’s arguably more straightforward than many of the other types of analysis described in the thesis). Online resources for this type of analysis are available (e.g., Bindfit on supramolecular.org). When analyzing solution-phase binding data, it is also advisable to obtain support for the proposed stoichiometry of complexation (e.g., by evaluating the qualities of fits to a range of potential binding models).

Chapter 6: the torsional angle of the nitro group is analyzed to make inferences about the existence of an O---O chalcogen bond (pp 159-160). Incorporating substituents para to the nitro group should influence the torsional potential about this C-N bond (through resonance) in addition to influencing the strength of the noncovalent interaction. It may be appropriate to include this qualification to the analysis.

Chapter 9: Important precedent for this chapter is not cited:

<https://pubs.acs.org/doi/pdf/10.1021/jacs.6b12745>. At the minimum, a reference to this work should be included. Ideally, the thesis would include a discussion of any similarities/differences between the approach taken in Chapter 9 and that reported by Beer and co-workers (the details are included in the SI of the JACS paper).

Chapter 9: On page 225, the author mentions that the center of the sigma hole is slightly offset from the extension of the Se-N bond. This effect is also evident in the geometries of the complexes described in Chapter 3. Is there an explanation for this behaviour?

The results of the energy decomposition analysis from chapter 9 (dispersion and electrostatics account for 80% of the chalcogen bonding interaction) seem to be at odds with the conclusion from chapter 3 (N---Se interaction is driven primarily by orbital overlap). Is there an explanation for this difference?

Minor issues (grammar/style/typographical errors):

- Page 29: complementary vs complimentary
- Page 45: Analytical analysis is perhaps not an ideal title for this section.
- Chapter. 6 (page 160): it is not clear what is meant by 'libration of the nitro group' (this is generally a term from the astronomy field).
- Chapter 7: Van-der Waals (no dash is needed here).
- Chapter 7: avoid 'splicing' sentences with commas: e.g., "In medicinal chemistry the chalcogen bond is considered... , this property is currently being exploited..."
- Chapter 9: a few grammatical issues ('Namely, electrostatics, induction, and dispersion' [page 223, not a sentence]; it's relatively small size [page 229]).