

Graduate Research Examinations
Student Administration | Student & Scholarly Services
The University of Melbourne,
Victoria 3010
Australia

To Whom It May Concern:

PhD Thesis examiners report

Thesis Title: **Investigations into Chalcogen Bonding**

Author: Thomas Fellows

Supervisor: Professor Jonathan White

This thesis describes a series of different investigations of Chalcogen bonding, with the main focus on selenium in ebselen and related molecules. The potential for bonding of this type with oxygen was also investigated in a series of o-nitro phenyl oximes. The investigations used several different methods, involving synthesis of new compounds and analyses via single crystal x-ray diffraction (including charge density studies), solid-state selenium NMR, and computational methods. These studies were impacted by restricted access to laboratory facilities through several COVID19 induced lockdowns. Given these restrictions, the quantity and quality of the work is commended. This thesis is one of the most well written that I have read, and is remarkably free of typographical errors. Congratulations on an excellent thesis!

The thesis gives a good introduction to the field of chalcogen bonding. The donor mediated population of the $\sigma^*(X-X)$ orbital, and the concomitant bond lengthening clearly has parallels with addition and substitution reaction transition states. These bonds clearly have numerous potential and real applications in materials and supramolecular chemistry, where they can be added to the interactions that mediate structure formation. It also plays an important role in catalysis and in protein interaction where it can be an important ancillary interaction between the naturally electron rich amide carbonyl oxygen and disulfide bonds. I would note that there are some references with abbreviations of the journal title that I found in this chapter, where the full name is used more generally. This should be checked in the remainder of the thesis.

The second chapter is a summary of the general experimental methods used throughout the remainder of the thesis. These were presented in a very clear manner that was easy to understand. I would have perhaps liked there to be more of a critical analysis of the computational methods used, including their problems. The section on charge density studies was particularly interesting, although, again this could have been more critical. What are the requirements for the quality of data required? One issue with these refinements is the potential for over-parameterisation. What were the criteria used to determine if the data was of sufficient quality and quantity to allow charge density determinations to be made? Disorder can also be a significant issue here. What are the limits of the methods used in this thesis? The description of the solid-state NMR was also informative. Where was Figure 2.12 sourced from? It does not appear to have been drawn by the author.

The third and fourth chapters summarise the investigation in the solid state of structures containing benzoselenazolinone derivatives complexed with Lewis basic molecules. This was done with a mixture of crystallographic and solid state ^{77}Se -NMR. Chapter 3 appears to be drawn directly from a paper published in *CrystEngComm* (which should be abbreviated as such), while Chapter 4 is additional data that is more extensively investigated. This approach has been used throughout this thesis, with 4 papers published already (some with an additional results chapter). I found this organisation frustrating to read, and problematic for several reasons. A Thesis prepared for PhD should be largely the work of the author, with any additional studies appropriately attributed to the person who did the work. I note that this has been described in the preface in terms of the research results. However, the *writing* should also be the work of the candidate, and it is not clear to me that the papers repeated in the thesis

were written entirely by the candidate. In addition to this, the work described in some cases, while at an appropriate level of detail for publication in a journal, does not reach the standard required for a PhD (see below). This approach lacks detail, and by necessity creates repetition in the introduction sections. This could easily have been overcome by combining chapters 3 and 4 together, and reorganising the material, with a similar approach used throughout. I think that this would have improved the thesis. Having stated this, the work described is of a high standard, and given the quantity and quality I will accept this.

The synthesis of benzoselenazolinone derivatives is detailed, although the diagrams of Scheme 3.1 should be altered to make the Se-N bond more visible. These are literature compounds, apart from **3**, which results from a dimerisation reaction. In my view this compound has not been adequately characterised for a new compound, with only ^1H - and ^{77}Se -NMR and a melting point taken. A ^{13}C -NMR and mass spectrum result need to be included. It is also disappointing to see the lack of assignment of ^1H -NMR spectra throughout the thesis, this is perhaps a feature of the publication in a crystallography journal (*CrystEngComm*) where this is not required. These molecules were co-crystallised with nitrogen atom containing Lewis bases, and their structures determined using single crystal X-ray diffraction. This data clearly shows the formation of Chalcogen bonding. The labels for the structural parameters in Table 1 are not clear, referring to the numbering scheme in the crystal structures – this is not shown anywhere in the Thesis. I note it was available in the supplementary information in the journal article. The same is true of the powder patterns, these need to be included in the thesis. Intriguingly there is a clear enhancement of the Chalcogen bonding arising from hydrogen bonding to an adjacent carbonyl. It should be made clear in the text how hydrogen atoms were treated in the refinements. I liked the use of bond difference sigma to display the difference between comparable values, this made determining the statistically relevant values much easier.

Chapter 4 investigates the effects outlined in chapter 3 in more detail. The first line of states that in the previous chapter it was established that Ch-bonding dominates packing through Se...O interactions, I could not find this in Chapter 3. The trend was investigated using different pyridine based Lewis bases, and substitution of the benzoselenazolinone derivatives in the aromatic ring. The position of substitution should be explicitly stated. The crystals grown were used as part of a charge-density investigation, with different approaches outlined. I would like to have seen more detail about what criteria were used to decide which method to use, “low angle data” and “quality of data” should be defined. I would have liked a more detailed description of the methods applied to the structures. The Hammett plots of the data were very informative, and clearly show trends relating the bond lengths with electron density of the ring systems. This chapter would have benefitted from a description of the other interactions involved in the crystal packing, which could clearly also affect the structure, and therefore the measurements made. Is it possible to see the trend for Ch-bonding in the carbonyl bond length? This should be elongated as depicted in Figure 4.1. Solid-state NMR was also used to investigate the complexes, with ^{77}Se measurements proving particularly useful. Allowing the calculation of the chemical shift anisotropy on the selenium atom. This was even done using an oriented single crystal. These crystals are of sufficient size to allow neutron diffraction, which would have added to the charge density studies, was this considered? The method used to display the crystallography data made it hard to compare the results, this would have been much easier to interpret in tabular form. Most troublingly, there is also no information about the charge-density analyses, making it impossible to determine how well the electron density was modelled. Is there really enough data available from a collection made with copper radiation?

Chapter 5 continues the investigation of chalcogen bonding in a series of o-nitro oximes. This is very interesting, as Ch-bonding is not normally considered for oxygen, usually it is only observed for heavier atoms (S, Se, etc). These molecules have the potential to form intramolecular Ch-bonds, and this have been investigated structurally using X-ray crystallography. Due to this chapter being copied from a communication published in Chemical Communications, it has similar general problems as those described above. In Table 5.1 the atomic numbering used needs to be explicitly outlined. Is there any effect of the Ch-bonding on the nitro group? This chapter also analysed crystal structures published previously, although these are only analysed briefly. The analysis of the charge density using QTAIM theory showed the presence of bond critical points indicating the presence of Ch-bonding in some cases. However, it is not clear if the planar geometry required for Ch-bonding causes interactions, or is itself a consequence of them. This is a little bit of a “chicken-and-egg” argument, but the ambiguity should be mentioned in the text. Why is it remarkable that these interactions form in air and water stable compounds? It is clear that these interactions do exist for oxygen!

Chapter 6 adds additional results to those described above. This begins with further analysis of previously published structures. The criteria used to find these in the Cambridge Structural Database should be given. Several structural analogues were also synthesised and analysed structurally using single crystal x-ray crystallography. Unfortunately the Charge-density of these was not able to be analysed in some of these due to data issues (which should be outlined explicitly). However, an interesting trend in the nature of the groups opposite the nitro group was analysed, which showed that electron donating groups in this site aided the

formation of the Ch-bonding interaction, although only just! Does this indicate that the effect in oxygen is more electrostatic than in heavier elements?

Chapter 7 investigates the behaviour of an ebselen containing molecule forming a cocrystal with pyridine (via a Ch-bond), and the thermal rearrangement of this into a different structure with a carbonyl-to-Se Ch-bond. The crystal structure of the non-pyridine containing molecule was determined using data from the Australian Synchrotron due to their small size. How this data was processed is not discussed. The synthesis of the derivative investigated is outlined, along with powder diffraction studies, which clearly show the change from one structure to another. A difference spectrum between the calculated pyridine-free structure and the observed pattern would also have been informative. This is an interesting study, and adds further weight to the Ch-bonding being structurally important.

Chapter 8 examines the potential for chalcogen bonding to aid minor-groove binding to DNA, which can be useful in radioprotective therapies. Unfortunately the desired analogue proved troublesome to synthesise despite numerous different approaches. One interesting observation was the trouble found in forming the acid chloride of picolinic acid. This is a commercially available compound that is commonly used. What was the nature of its decomposition? Due to these issues a related molecule could be synthesised, and its behaviour with a representative DNA oligomer investigated. Unfortunately it proved impossible to co-crystallise the derivative with DNA, so UV-vis titrations were used to measure interaction. Arrows should be added to these curves to indicate the changes in absorption. Ultimately these studies showed that the derivative formed co-valent bonds to the DNA which negated their potential as radioprotective molecules.

The final results chapter outlines the development of molecular mechanics software to allow chalcogen bonding to be included using a pseudoatom approach. Given the results from the previous chapters this addition to current computation molecular mechanics software is clearly warranted. In order to correctly determine the parameters for the pseudoatom, DFT calculations were made for different Lewis acids. These clearly give subtly different results, which should be explained in more details (eg Me₂S vs pyridine). The approach was validated against different models, including the ebselen complex of SOD1.

The final chapter is an overview of the previous sections that pulls together the results and makes some concluding statements. These were interesting, although fairly brief. I would have preferred to see more here.

In summary, I found this thesis to be of excellent quality, displaying clear original and critical thought. It contains several different analysis of Chalcogen bonding in different compounds, including involving oxygen, an unprecedented result. These analyses were made using a variety of different methods including X-ray crystallography (including Charge-Density analysis), solid-state ⁷⁷Se-NMR, UV-vis and a range of computational methods. The thesis is fantastically well written with only a few typographical errors, the research has been carried out logically and is coherently investigated, well referenced, and described. This original contribution contains a considerable number of results, which already form the basis for publications in peer reviewed high impact journals. The research described and Thesis meets the requirements of a PhD in Chemistry, and I believe that Mr Fellowes should be awarded a PhD. I have noted several typographical errors in my copy of the thesis which I can send on request.