

# Response to examiner reports

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## Investigations into Chalcogen Bonding

Thomas Fellowes

### Examiner 1

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).

Thank you for these references, they have now been cited in the introduction, and at relevant points throughout the thesis (see page 5 onwards).

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).

This has been corrected as much as possible throughout the thesis (see page 7 onwards).

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.

This is an issue that is endemic to energy decomposition analysis schemes, the investigation and explanation of which was considered outside the scope of the thesis. Within the SAPT scheme (which I believe is the most objective and physically grounded of all EDA schemes, and thus used throughout the work where a fully computational EDA is called for) this mutual polarisation effect is contained within the induction term. In NEDA (an extension of NBO theory, which is also briefly explored), this contribution is contained in the charge transfer component, but this is not well defined (NEDA is known to significantly overestimate charge transfer). I chose to take an experimentalist's view of the respective energy components, which borrows heavily from NEDA, where mutual polarisation is not a unique component but subsumed in a 'covalent' term, the magnitude of which we infer from endocyclic bond lengthening. I therefore think the electrostatic/covalent/dispersion distinction is valid throughout the thesis, except in the more computationally focussed Chapter 9, where SAPT is introduced.

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). <sup>13</sup>C NMR chemical shifts should be reported to the nearest 0.1 ppm.

Thank you, these have been corrected.

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.

This is a good point, and one which we intend to discuss further in an upcoming paper based on Chapter 4. The idea comes from the balance of repulsive forces (which should be fairly constant, decaying with  $r^{-12}$ ) and variable attractive forces (decaying with  $r^{-6}$ ). It naturally follows that increasing the magnitude of the attractive term increases the depth of the potential well, while also decreasing the equilibrium interatomic distance. It is probably true that there are limits to this approximation, however we have not encountered them. A comment has been added on page 77.

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](http://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).

Thank you for this recommendation. The analysis has been redone using Bindfit, which actually improved the fit for the Hammett relationship! (pp 109-110)

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.

This is an excellent point. Unfortunately I cannot see a method to effectively untangle this contribution from the overall geometry without resorting to quantum methods.

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).

Thank you for this reference, I was not aware of this work that had been done. It has now been cited and discussed in the introduction (page 227).

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? A brief note has been added to explain this (page 234).

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?

A brief note has been added to explain this (page 233).

Minor issues (grammar/style/typographical errors):

- Page 29: complementary vs complimentary

Corrected.

- Page 45: Analytical analysis is perhaps not an ideal title for this section.

This has been changed to 'Additional analyses'.

- 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).

Libration refers to a oscillating motion which in this case caused elongation of the thermal ellipsoids perpendicular to the plane of the ring. I feel this is a sufficiently common term in chemistry (common enough to merit a Wikipedia article), however I have added a qualifying note.

- Chapter 7: Van-der Waals (no dash is needed here).

Corrected.

- Chapter 7: avoid 'splicing' sentences with commas: e.g., "In medicinal chemistry the chalcogen bond is considered... , this property is currently being exploited..."

Corrected.

- Chapter 9: a few grammatical issues ('Namely, electrostatics, induction, and dispersion' [page 223, not a sentence]; it's relatively small size [page 229]).

These have been corrected.

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## Examiner 2

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.

Journal abbreviations have been double checked throughout and corrected.

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.

I believe that shortcomings of each method were adequately discussed where they were relevant, bearing in mind that this chapter is not meant to be a comprehensive review of these techniques!

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?

Generally the standard rules to avoid over-parametrisation are adequate (data to parameter ratio > 10). Suitability for multipole refinement was primarily judged by the residual electron density maps from an IAM refinement.

Disorder can also be a significant issue here.

Disorder can sometimes be modelled using highly restrained multipole models, however it is often found alongside other issues which preclude multipole refinement. In all cases, the quality was judged by residual electron density, taking into account disorder, and no disordered structures were found to be suitable for multipole refinement.

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.

I can't find the original source, I have replaced it with a better figure that is also appropriately cited (page 44).

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  $^{77}\text{Se}$ -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.

This is a valid criticism, and I suppose a stylistic choice. Given the publications were accepted, I was reluctant to change them, and this seemed to be the best way to present a thesis with publications.

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.

This has been done (page 54).

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  $^1\text{H}$ - and  $^{77}\text{Se}$ -NMR and a melting point taken. A  $^{13}\text{C}$ -NMR and mass spectrum result need to be included.

HRMS has been added to support the characterisation (page 63). Unfortunately a  $^{13}\text{C}$ -NMR spectrum was not able to be obtained as the compound had decomposed.

It is also disappointing to see the lack of assignment of  $^1\text{H}$ -NMR spectra throughout the thesis, this is perhaps a feature of the publication in a crystallography journal (CrystEngComm) where this is not required.

Perhaps also a philosophical choice. Assignment of spectra is necessarily subjective, and I think experimental methods should be restricted to fact. However, spectra for novel compounds have been assigned in relatively unambiguous cases.

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.

Numbering has been included in figure 3.1 (page 55).

The same is true of the powder patterns, these need to be included in the thesis.

These are now shown with the crystallographic data (pp 64-71).

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.

A comment has been added in Chapter 2 regarding refinement of H atoms (page 47).

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.

This has been clarified (page 76).

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.

This has been added (page 78).

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.

A clarifying note has been added to quantify these statements (page 79).

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.

The only other significant forces are C-H/ $\pi$  and  $\pi/\pi$  interactions, which are substantially the same between structures, and would not effect the relevant bond lengths in any case. I therefore omitted any further discussion of them.

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.

This is a good point, which is briefly alluded to in fig 4.11. A trend could be expected, however it was not visible in the noise in the data.

Solid-state NMR was also used to investigate the complexes, with  $^{77}\text{Se}$  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?

I am not sure neutron data would have added a great deal to the charge density studies, beyond the accurate determination of atomic coordinates, which we determined using high angle data instead. It would however be very interesting to investigate any radical character at the selenium, perhaps using a TEMPO Lewis base.

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.

Refinement statistics of the multipole model have been included.

Is there really enough data available from a collection made with copper radiation?

This is a good question. We believe there is, in the presence of extra information (i.e. from a wavefunction calculation). The valence electron density is contained in the low angle reflections, and the charge density parameters can be refined separately to preserve the data to parameter ratio.

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.

A diagram has been added to explain this (figure 5.2, page 148).

Is there any effect of the Ch-bonding on the nitro group?

We didn't see any structural changes in the nitro group, however we noted the presence of sigma holes visible on the nitro oxygen atoms, which could potentially also participate in Ch-bonds.

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.

This is true, and I comment on this in the chapter.

Why is it remarkable that these interactions form in air and water stable compounds?

Previous work has only focussed on Ch bonding in molecules such as OF<sub>2</sub> and FNO<sub>2</sub>, the utility of which is very limited by their extreme reactivity.

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?

I don't think it's possible to infer the magnitude of energetic components from this data. Another way to consider it is that electron donating groups opposite the nitro increase the energy of the lone pair, thus improving orbital overlap. Does this make it more covalent? I don't believe so. Just two sides of the same coin.

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.

This has been added to Chapter 2.

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?

Treatment of picolinic acid with thionyl chloride led to the formation of a black tar. Perhaps an issue with our reagents? Or we possibly needed to pre-form the hydrochloride salt.

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.

This has been done (page 208).

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 Me<sub>2</sub>S vs pyridine).

I believe this was adequately covered in the energy decomposition analysis section.

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 <sup>77</sup>Se- 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.