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PhD Review

Review of the PhD manuscript of Agnieszka POULAIN

Untitled "*Experimental investigation of the charge density distribution in the crystals of 4-nitroimidazole derivatives*"

Mrs Agnieszka Poulain has prepared a joint PhD between Adam Mickiewicz University (Poland) and Université de Lorraine (Nancy, France) under the supervision of Professors Maciej Kubicki and Claude Lecomte. The main part of the work was realized in the CRM^2 (Cristallographie, Résonance Magnétique et Matériaux) laboratory which is famous throughout the world for the experimental electrons density studies from high resolution X-ray diffraction experiments. The title of Mrs Poulain thesis is "Experimental investigation of the charge density distribution in the crystals of 4-nitroimidazole derivatives". This study is essentially experimental but a part of this work is dedicated to the methodology development of the diffraction data refinement in order to obtain reliable molecular properties. The results presented in this manuscript are excellent and the applicant efforts are amazing since she carried out charge densities studies on 5 organic molecules. The manuscript of Agnieszka Poulain (275 pages + an appendix with Tables of crystallographic and charge density parameters + a DVD Rom disc containing additional data) is excellently written in English (very few errors) and very didactic. The presentation is clear and the figures and Tables are well presented and accordingly illustrate the text and the results. The literature references are exhaustive and updated.

The work of Agnieszka Poulain is really impressive for the three years of the PhD preparation. The data collections, at several temperatures, for five molecules of nitroimidazole derivatives are excellent and the results too. Nevertheless, the applicant emphasizes traps and pitfalls in the data refinement in order to get a physical property like dipole moments. I recommend this manuscript for all beginners in the field of charge density studies. Agnieszka Poulain carried out X-ray diffraction measurements on both single crystals and powders to determine the cell parameters and follow the phase transition.

The manuscript is divided in 4 parts: Methodology of X-ray diffraction (I), Aim of the studies (II), Results and discussion (III) and General conclusions (IV). Part I is dedicated to the general background of the charge density studies from the data collection strategies to the problematic refinements (restraints in least-square refinements, the use of the R_{free} factors to get a robust results, anharmonic thermal smearing and atomic disorder). The electron density model used here is that of Hansen-Coppens mutipole model. The way to analyze the electron density is also presented through the Bader's topological theory based on the gradient and the Laplacian of the electron density distribution. The general formulae for the determination of the electrostatic properties (namely, electrostatic potential (ESP and not "EPS" in e.$Å^{-1}$ and not "e.$Å^{-3}$" unit found in all the text) and electrostatic interaction energy) are also given. In Part II, the molecular properties and also the synthesis of the studied nitroimidazole derivatives are presented. Particular highlights of the encountered intermolecular interactions in the studied nitroimidazole derivatives (H bonds, Halogen bonds, dipole-dipole interactions, H···H contacts and $\pi\cdots\pi$ stacking) are given. The results of the charge density studies of the five molecules are discussed in Part III. The reading of this part is absolutely not boring and the applicant does not present the results repetitively. For each molecule, the particular encountered problems are emphasized and solved in the best manner: anharmonicity for molecule 1, dipole moment estimate for molecule 2, disorder (C-N triple bond and Br) for molecule 3 and Chlorine electron density refinement for molecules 4 and 5.

My main comments and critics are as follows:

- In most cases, I would prefer the dynamic deformation density maps over the static ones especially when thermal smearing is discussed.

- The gradient lines and electrostatic potential maps are poorly commented and discussed. Electrostatic complementarity for example is not discussed for interacting molecules in the unit cell.
- P. 138-139: it is not sure that the experimental and theoretical parts of the electrostatic energies are equal (sum of positive and negative contributions).
- P. 157: the theoretical dipole moment is chosen as a reference but its estimate is dependent on the orbital basis sets. My opinion is that, since the measure of the dipole moment was not achieved, fitting the high resolution based dipole to the theoretical one is questionable. However, the revealed effects of the level of the atomic multipole used and the electron density parameters of the peripheral H atoms are real and well discussed. This can be discussed during the defense of the PhD.
- I really appreciate the Part IV of the manuscript and the conclusions and perspectives presented by the applicant.

During her preparation of the PhD, I am convinced that Agnieszka Poulain has gained a high level of professionalism in the field of the experimental electron density in molecular compounds. This is clearly demonstrated when reading such an almost perfect manuscript. I totally agree for her oral presentation to defend her thesis in order to deserve the title of "Doctor of Philosophy".

Châtenay-Malabry, January 16th, 2013.

Nour Eddine Ghermani, *Professor*