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REVIEW OF THE PHD DISSERTATION BY MRS AGNIESZKA POULAIN

ENTITLED

EXPERIMENTAL INVESTIGATION OF THE CHARGE DENSITY DISTRIBUTION IN THE CRYSTALS OF 4-NITROIMIDAZOLE DERIVATIVES

The PhD dissertation by Mrs Agnieszka Poulain has been supervised by Prof. Claude Lecomte (Lorraine University, Nancy, France) and Prof. Maciej Kubicki (Adam Mickiewicz University, Poznań, Poland). It aimed at charge density distribution in crystals of 4-nitroimidazole derivatives, hereafter (**I**), (**II**), (**III a**), (**IV**) and (**V**), the detailed nomenclature is given in the dissertation. Actually, crystal and molecular structures of (**I**) – (**V**) were determined earlier with standard resolution by Kubicki and co-authors and by use IAM (Independent Atom Model).

The task to be carried out was quite complex, namely after the re-determination of all the structures (**I**) – (**V**) applying the IAM approach she did the Hansen-Coppens multipole refinement. Diverse constraint and restraint conditions were checked, careful modeling of hydrogen atoms was done, etc. Finally, on the basis of the AIM (Atom In Molecules) topological analysis of electron density (such as critical points, bond paths localized between interacting molecules, total electron density at the critical points, Laplacian values etc.) she could characterize substituents effect on the imidazole ring as well as quantitatively prioritize intermolecular weak interactions such as hydrogen bonds, dipolar interactions, halogen bonds and van der Waals contacts.

When working on the subject she ran up against a number of difficulties or points that had to be solved beyond standard procedures if one can consider the multipolar refinement as a standard one at all.

For that reason a good part of the thesis is of methodological character often of pioneering nature performed to find the best way to reach a good model. Let me mention some interesting points:

- Free R factor calculations carried out for (**I**) to assess if dissimilarities of the charge density between the two symmetry independent molecules are reliable, as well as to find the optimal restraints level. It was one of the first attempts to use R_{free} calculations in the experimental charge density modeling of small organic molecules although this approach is used in electron density modeling for protein crystals.

- Modeling of a special kind of disorder, that is the solid solution of (**III a**) which was accidentally obtained in the recrystallization process of (**III**). This special kind of disorder discovered for (**III a**) was modeled by means of the multipolar parameters transfer from similar molecules. Actually, the modeling of solid solution disorder in multipole approach is a pioneering research.

- Mrs. Poulain performed successfully anharmonic refinement (Anharmonic Nuclear Motion) for some atoms that produced high residual density peaks arranged in a "shashlik - like" pattern or a significant , unreasonable distortion of the deformation density. There were two nitrogen atoms of the amino groups and one nitro group in (**I**), also for two chlorine atoms in structures (**III a**) and (**V**).

- To verify the specific nuclear motions and necessity of modeling them as anharmonic parameters the Author performed several diverse low temperature measurements for (**I**): high resolution data were measured at 10 K and 100 K at the Agilent Technologies devices; then, powder measurements between 23 K and 298 K when looking for a phase transition and finally a pioneering measurement at 35 K and 70 K at a four circle diffractometer with the Nonius Kappa CCD detector and with helium-bath orange cryostat designed for helium regain.

Mrs. Poulain also carried out extended calculations of the dipole moment. Joined experimental (from X-ray diffraction) and theoretical (from DFT calculations) data refinement were performed only for molecule (**II**) in order to determine the best initial set to calculate the dipole moment with its magnitude and direction similar to the one obtained from theory. She found a set of restraints and constraints for three tested models of electron density

distribution: the Hansen – Coppens multipole model, virtual atom model and kappa model for each, the theoretical and experimental data.

Getting down to the assessment of the thesis:

- I would emphasize careful and professional course of the low-temperature diffraction experiments and a pioneering data collection with the low temperature helium-bath orange cryostat device;

- Diverse approaches to the multipole refinements, careful modeling of hydrogen atoms, anharmonic nuclear motion modeling applied to some atoms of the compounds under investigation, free *R* factor calculations, carefully balanced constraints and restraints, everything very well done and critically talked over. All these efforts and strategies result in very good values of final indicators such as multipole model *R* factors, rigid bond tests, flat residual electron density maps, clear static deformation electron density maps. I appraise the methodical part of the dissertation very well. Some of the refinement strategies are of an inventive character;

- Crystal chemistry aspects: description of the particular disorder in the structure of (**III a**) as solid solution of (**III**) and bromo-derivative that was evidenced by the refinement. The multipole modeling of such specific disorder hasn't been carried out earlier - Mrs. Poulain is the first who did it. On the basis of topological parameters she performed quantitative classification of intermolecular interactions. A very interesting achievement. Can the quantitative criteria of classification be applied to the other molecular crystals with similar kinds of interactions?

- And finally, the dipole moment: when modeling using theoretical calculations, the experimental value should be this one that is referred to. Mrs. Poulain refers to the dipole moment value that was obtained from indefinite theoretical calculations.

- It should be emphasized here that many strategies of modeling applied in the dissertation are based on recently published papers.

- Mrs. Poulain is a co-author of three papers published in 2011 – 2012, in the international journals with high impact factors.

- The thesis has been written in English, contains about three hundred pages, has been constructed very clearly .

In summary, results presented in the thesis are outstanding, all the conclusions are justified by strong arguments and critical discussion, the scientific level is of the worldwide character, a part of results has been already published in the international journals with high impact factors.

In my opinion the thesis deserves to be rewarded. I also state that it meets the all requirements in accordance with the article no. 13 of the act of March 14, 2003 on scientific degrees and scientific titles.

In conclusion, the above statement qualifies Mrs. Agnieszka Poulain to pass the further parts of the PhD procedure.

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