Załącznik 3

Annex 3

SELF-PRESENTATION

1. Name Family Name

Bartosz Zarychta

2. Scientific degrees

2002 Master of Science Faculty of Mathematics, Physics and Chemistry, University of Opole, Opole.

2008 Doctor of chemical science, Faculty of Mathematics, Physics and Chemistry, University of Opole, Opole. Ph. D. dissertation entitled: *Sructure and phase transitions in selected halogenoantimonates(III) and bismuthates(III) with organic cations.* Promotor: prof. dr hab. inż. Jacek Zaleski

3. Information about previous and current employment

1st October 2002 - 30th September 2008 Assistant, Institute of Chemistry, Faculty of Mathematics, Physics and Chemistry, University of Opole.

1st April 2006 - 31st December 2006 Assistant, CRM^2 Laboratory, Université Henri Poincare, Nancy I, France.

29th January 2015 - 28th January 2016 Postdoctoral position**,** Department of Chemistry and Biochemistry, Toledo University, Toledo, OH, USA.

1st October 2008 - till now Adjunct, Faculty of Chemistry, University of Opole.

4. Selected achievements pursuant to article 16 paragraph 2 of the Act of 14 March 2003 on Academic Degrees and Title as well as on Degrees and Title in the Field of Arts (Dz. U. [Journal of Laws] of 2016 item 882, as amended in Dz. U. of 2016 item 1311):

A) Title of scientific achievement:

MODELLING OF CHARGE DENSITY DISTRIBUTION AS A TOOL OF CRYSTAL STRUCTURE OPTIMISATION

B) List of publications included in the scientific achievement arranged according to the article 16 paragraph 2 of the Act

The scientific achievement consists of a series of 6 original papers (**H1** - **H6**). The references to these papers are denoted with the H prefix. The total Impact Factor (IF) calculated according to the publication date (unless otherwise indicated) by using the Journal Citation Reports database is equal 21,814 (MNiSW points = 205) for this series. The total citation number for the series of publications constituting scientific achievement is equal to 40 without autocitations (19/02/2019). The corresponding author's name is indicated with the star sign (*).

Nº **Authors, title, volume, year, pages, impact factor from the year of release, estimate of own contribution**

H1 **Zarychta, B.**, Zaleski, J., Kyzioł, J., Daszkiewicz, Z., Jelsch, C.*: Charge-density analysis of 1-nitroindoline: Refinement quality using free R factors and restraints (2011) Acta Crystallographica Section B: Structural Science, 67 (3), 250-262. (IF$_{2011}$ = 2.286, MNiSW = 25)
I planned the work. I performed the XRD experiment. I made all refinements and calculated properties of the charge density distribution, structural and charge density analysis. I interpreted results, wrote manuscript. I edited the publication. I rate my percentage contribution as 80%.

H2 Gajda, K., Daszkiewicz, Z., Kozubek, E., Ejsmont, K., **Zarychta, B.***: Theoretical multipolar atom model transfer in nitro-derivatives of N-methylaniline (2014) Crystal Growth and Design, 14 (11), 5737-5748. (IF$_{2014}$ = 4.558, MNiSW = 40)
I planned the work. I performed XRD experiment. I made refinements and calculations, structural and charge density analysis. I supervised calculations led by Ph.D. candidate Katarzyna Gajda, M.Sc. as her auxiliary supervisor and M.Sc.

candidate Ewelina Kozubek as her supervisor. I interpreted results. I edited the publication. I made the corrections to the work after reviews. I rate my percentage contribution as 80%.

H3 **Zarychta, B.**, Lyubimov, A., Ahmed, M., Munshi, P., Guillot, B., Vrielink, A., Jelsch, C.*: Cholesterol oxidase: Ultrahigh-resolution crystal structure and multipolar atom model-based analysis (2015) Acta Crystallographica Section D: Biological Crystallography, 71, 954-968. (IF_{2015} = 2.512, MNiSW = 45)

I made final refinements of experimental data, calculated properties of the charge density distribution, transferred multipolar data. I performed the analysis of cofactor-protein hydrogen bonds. I analysed an electrostatic potential and a secondary structure of the Cholesterol oxidase molecule. I interpreted results and wrote manuscript in 'Protein charge-density model' and 'Electrostatic potential' parts. I rate my percentage contribution as 60%.

H4 Chua, Z., Gianopoulos, C.G., **Zarychta, B.**, Zhurova, E.A., Zhurov, V.V., Pinkerton, A.A.*: Inter- and intramolecular bonding in 1, 3, 5-triamino-2, 4, 6-trinitrobenzene: An experimental and theoretical quantum theory of atoms in molecules (QTAIM) analysis (2017) *Crystal Growth and Design*, 17 (10), 5200-5207. (IF_{2017} = 3.972, MNiSW = 40)

I participated in experiments, refinements and calculations of experimental and theoretical charge density properties. I participated in interpretation of results. I rate my percentage contribution as 30%.

H5 Chua, Z., **Zarychta, B.**, Gianopoulos, C.G., Zhurov, V.V., Alan Pinkerton, A.*: Revisiting the charge density analysis of 2,5-dichloro-1,4-benzoquinone at 20 K (2017) *Acta Crystallographica Section B: Structural Science*, 73 (4), 654-659. (IF_{2017} = 6.467, MNiSW = 30)

I participated in experiments, refinements and calculations of experimental and theoretical charge density properties. I participated in interpretation of results. I rate my percentage contribution as 40%.

H6 Dziuk, B., Gianopoulos, C.G., Ejsmont, K., **Zarychta, B.***: Self-assembly

mechanism based on charge density topological interaction energies (2018) *Structural Chemistry*, 29, 703-713. (IF_{2018} = 2.019, MNiSW = 25)
I planned the work. I performed the XRD experiment. I supervised refinements and calculations led by Ph.D. candidate Błażej Dziuk, M.Sc. as his auxiliary supervisor. I interpreted results. I edited the publication. I made the corrections to manuscrript after reviews. I rate my percentage contribution as 80%.

Copy of above publications can be found in Annex 4. Statements of all co-authors, defining individual contribution can be found in Annex 5. Two co-authors of **H1**, i.e. Prof. Jacek Zaleski and prof. Janusz Kyzioł are dead, and their statement is signed by Faculty of Chemistry Dean, Prof. Piotr Wieczorek, on their behalf.

C) Report on the objective and the results of the research together with the discussion on potential applications

INTRODUCTION

The crystal engineering and molecular modeling has been a particularly fast growing area of chemistry leading to new materials with controlled and predictable properties. The influence of crystallography on these disciplines is uncontested, and its impact on society in general is increasing at an accelerated pace due to numerous scientific applications. With the availability of high brilliance third generation synchrotron sources and ultra–low temperature cryo–crystallography (T≈100 K with a nitrogen stream or even T≈10–30 K with helium) the quality of diffraction data is continuously improving both in terms of signal to noise ratio and in resolution. The possibilities in computational chemistry/biology (quantum calculations and classical molecular simulations) are also growing with the regular increase of computing power. Due to this unstoppable progress in crystallography and in computing power, the area of charge density analysis in small molecules has already attracted enormous attention to the scientific community and it is expected to become much more intense in the future. Excellence of research does not go unnoticed; scientists continue to make remarkable progress in these areas.

The analysis of charge densities can be derived experimentally in the crystalline state from ultra-high resolution X-ray diffraction (Coppens, 1967, 1997, 1998; Lecomte, 1995; Koritsanszky and Coppens, 2001) and theoretically from quantum-mechanical calculations for isolated molecules or/and in the solid state. Moreover, the charge density model can be obtained through a transfer of atomic multipolar parameters from experimental (Zarychta *et al.*, 2007; Domagała *et al.,* 2012) and theoretical (Volkov *et al.,* 2007; Dominiak *et al.,* 2007; Dittrichet *et al.,* 2006) databanks. Brock and co-workers originally proposed the transferability in 1991 (Brock *et al.,* 1991). The atomic multipole parameters refined from the diffraction data of perylene were used to improve the estimation of molecular vibrations in naphthalene and anthracene crystals. The method is based on a chemical assumption that the charge density is similar in different (but related)_molecules and crystal environments. In such an approach, the specific electron properties are neglected, *e.g.* distortions of electron density distribution due to the contribution of mesomeric structures in molecular resonance hybrid or polarisation of atoms and valence densities due to the chemical contexts such as in the case of strong hydrogen bonding. Nevertheless, the transferred multipolar parameters to the spherical atom model of the initial molecule structure should significantly improve the crystal structure and result in more accurate and physically meaningful thermal displacement parameters. The charge density parameters can be also transferred from multipolar atoms libraries. Currently there are three databanks developed by the charge density community: one experimental (crystallographic) ELMAM/ELMAM2 - Experimental Library of Multipolar Atom Model (Zarychta *et al.,* 2007; Domagała *et al.,* 2011) and two libraries derived from theoretical computations: UBDB – University of Buffalo DataBank aspherical–atom (Volkov *et al.,* 2007; Dominiak *et al.,* 2007) and Invariom database (Dittrich *et al.,* 2006). The comparison of the libraries is listed in Table 1. The theoretical libraries are based on calculations performed *in vacuo*, thus they do not take into account intermolecular interactions such as hydrogen bonds (HB) or/and polarisation of the electron density cloud due to the HB. The experimental databank is also not perfect as the averaged experimental parameters carry only average information of hydrogen bond effects and charge density polarisation in mesomeric hybrids. Therefore, the individual and unique character of the electronic structure and solid state structure of the molecule under investigation might be mistreated. Recently, Capelli and co-workers (Capelli et al., 2014) introduced the Hirshfeld Atom Refinement (HAR). In this method the pseudo-atom (Dittrich *et al.,* 2013) approach has been used for the unconstrained X-ray refinement of all structural parameters including positional and anisotropic displacement parameters for H-atoms. In these studies, the H-atom positions, interatomic distances and H-atoms ADP's have been significantly improved.

Table 1.
The comparison of currently available multipolar parameters databanks.

	Invariom database	**UBDB**	**ELMAM/ELMAMII**
Transferability 'cutoff'	Empirical rules	Statistics	Empirical findings/statistics
Database construction	Geometry optimizations of model compounds	Single–point energy calculations of structures from the CSD	Multipole refinements of high–resolution X–ray data
Method used	B3LYP, basis D95++(3df,3pd)	B3LYP, basis 6–31G*	X–ray diffraction
Main aim	Structure refinement and property calculation	Structure refinement and property calculation	Structure refinement and property calculation
Known strengths/weaknesses	Does not include effects of hydrogen bonding	Does not include effects of hydrogen bonding	Includes average effect of hydrogen bonding
	Easily extendable to new chemical environments	Easily extendable to new chemical environments	Experiment required for extension database

The method does not suffer from the necessity of the use of the generalized multipolar databanks as electron density distribution is continually adjusted to the changes in geometry for the molecule under investigation. Nevertheless the authors indicate some limitations of the approach. The HAR method uses molecular wave functions, so the application to network solids may not be ideal and the method might require use of the calculated periodic wave functions to be useful for solid-state analysis.

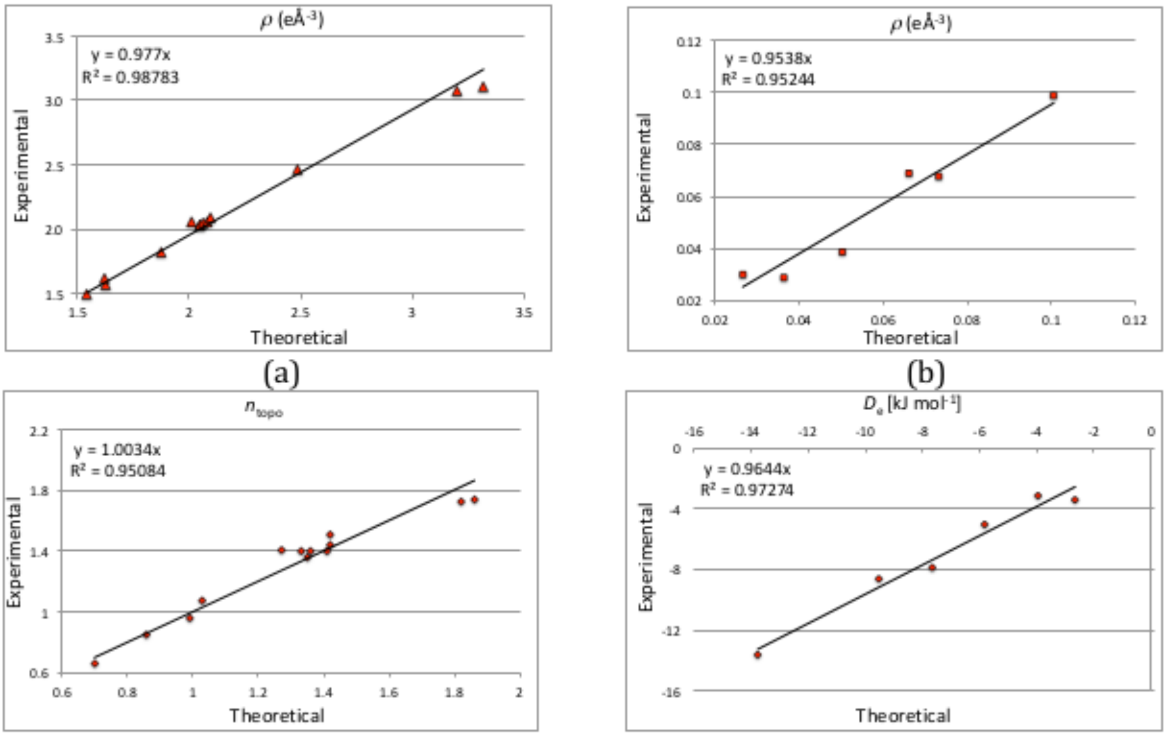
RESEARCH OBJECTIVE AND DISCUSSION OF RESEARCH RESULTS

Charge density analysis has been the object of my study throughout my scientificcareer. Currently, modeling of experimental and/or theoretical charge densities has gained enormous attention. Especially the latter as these became easily accessible due to increasing computational power and advancement in computational methods. They can serve not only as the source of analysis but also as the benchmark reference data for experimental research.

Based on my research and experience, which I acquired by cooperation with international partners, I proposed a practical and effective method of theoretical multipolar atom model (MAM) transfer by the use of calculated structure factors from the periodic wave functions for improving the independent atom model (IAM) and permitting meaningful charge density analysis. The crystal structure from an X-ray diffraction experiment is used as input for the IAM refinement as well as the periodic solid-state theoretical calculations. The main idea of the proposed method is to replace, without significant experimental and computing costs, the spherical atom model by the multipolar model and gain knowledge about the charge density distribution of the molecule under investigation. The MAM refinement can be useful not only for chemical properties description and verification, but also, improvement of the molecular geometry and description of thermal motion. This will result in better figures of merit, such as a lower crystallographic *R* factor and in more accurate phases than a traditional IAM refinement.

1. Optimisation of charge density model and molecular structure

In the case of charge-density analyses of small molecules, the required experimental resolution should be less than 0.5 Å. With such resolution stereochemical restraints are generally not necessary, except for hydrogen and disordered atoms. Nevertheless, when in-house equipment is used for data collection, the use of stereochemical restrains may be required, due to difficulties obtaining such high data resolution. This should be made with caution and critical examination of results at all stages of data refinement. In the case of charge density analysis of 1-nitroindoline (**H1**) the sample was measured using a CCD detector, where the known problems with integration of strong, low-angle reflections and high-angle kα_1 and kα_2 splitted reflections are proven (Zhurov *et al.,* 2008). The initial experimental charge density model left much to be desired and the theoretical data became very useful as a reference in modeling the experimental data. Within the **H1** paper, in cooperation with dr. Christian Jelsch at the Henri Poincare University (France), I have proposed a method of evaluation of the restrained charge density model. The evolution was based on the R-*free* refinement, which is routinely used in protein crystallography. In our approach, a series of comprehensive R-*free* refinements were carried out using different values of standard deviations ranging from 0.0001 up to 0.1 for the charge-density similarity restraints, which makes chemically equivalent atoms bear similar charge densities. The expansion/contraction coefficients (κ and κ'), valence and multipolar populations were regrouped in these similarity restraints. Local symmetry restraints (i.e. one or two mirror planes per atom) were also applied to the atomic multipolar charge densities and different weights were tested. The lowest values of the averaged R-free factors were considered to yield the best-restrained model, which were then applied in the final refinement. This method yielded a well-modelled electron-density distribution of the molecule, which is comparable to that obtained from the theoretical computations. The static deformation electron density grids obtained from theoretical and experimental multipole modeling displayed a correlation coefficient of 87% and a root mean-square (r.m.s.) quotient of 0.92. Moreover, the correlation between the values of parameters from the charge density analysis is even better (Fig. 1). The values of Pearson correlation coefficients between experiment and theory for the total charge density at the Bond Critical Points (BCPs) of intra- and intermolecular interactions, topological bond orders and intermolecular interactions dissociation energies are in the range from 0.95 to 0.98.



(a) (b) (c) (d)

Figure 1. Correlation between experiment and theory of (a) total charge density at BCPs of intramolecular interactions; (b) total charge density in BCPs of intra and intermolecular interactions; (c) topological bond orders and (d) intermolecular interactions dissociation energies for 1-nitroindoline (**H1**).

The study suggests that appropriate weighting applied to the charge-density restraints can reduce observed artefacts and make the final result physically reliable and meaningful. Moreover the proposed approach can be considered to be a novel

(iv) refinement of the atomic coordinates and thermal displacement parameters against experimental structure factors with fixed transferred multipolar parameters (final MAM refinement).

It turned out that this approach has some remarkable advantages *e.g.* it showed enhancement in statistical indexes. The reliability factor (RF) was improved by 45%, 39%, and 48% for *ortho*, *meta* and *para* respectively. The residual electron density maps further demonstrated the improvement. After IAM refinement, some residual density remained systematically on the covalent bonds, beyond 0.20 $eÅ^{-3}$, whereas after MAM refinement very little residual density was observed. The improvement of X–H distances toward the average values obtained from neutron diffraction (Allen *et al*., 1992) was striking, and the value of the residual factor indicates that the rigid-body (Hirshfeld, 1976) behaviour of the atoms was better described in MAM by the modeled ADPs. Furthermore, the result of the refinement with multipolar parameters was physically acceptable and the vibrational parameters were properly derived. Also the method allowed me to perform charge density analysis of the studied compounds. In all three molecules, the aromatic rings are deformed by resonance effects and, in the case of *ortho*, also deformed by the steric hindrance between the nitro and methylamine group. The contribution of the quinoid- like mesomeric structure in the resonance hybrid for the *ortho* and *para* derivatives was also observed by the corresponding bond orders. Similar effects were observed for the geometries obtained from quantum-mechanical calculations for the isolated molecule(s). Upon careful examination of the molecules electronic surroundings in all three structures, a significant number of intermolecular interactions have been revealed. The interactions are relatively weak. The topological properties of the intermolecular contacts at their BCPs were compared to the quantitative analysis of contacts derived from Hirshfeld surfaces (Spackman and Byrom, 1997; Spackman and McKinnon, 2002). Surfaces and positions of critical points exhibited coherent features. The comparison showed that the weakest contacts do contribute meaningfully to the crystal packing, however the crucial influence in crystal packing results from the O···H interactions.

Positive reception of the **H2** publication encouraged me to suggest the use of my proposed approach in the Ph.D. study of Błażej Dziuk, M.Sc. The initial topic of his thesis was focused on structural characterisation of supramolecular synthons in a series of organic salts composed of carboxylic acids and amines (aliphatic and aromatic). I came up with an idea to classify the synthons not only structurally, but also energetically, using charge density analysis provided by the MAM method (**H2**). The supervisor of Błażej Dziuk, prof. Krzysztof Ejsmont approved the idea and I was appointed as the Ph.D. student's auxiliary supervisor. The registered title of his Ph.D. thesis is "*Structural and electronic analysis of supramolecular structures in selected salts of carboxylic acids with amines*".

Crystals of salts composed of carboxylic acids and amines are perfect examples of the application of functional groups wherein the resulting crystal structures are stabilized by charge-assisted hydrogen bonding mediated by proton transfer. These are characterised with clear directionality, and a wide variety of possible cation-anion combinations (Sakai *et al.,* 2008). In the structure of ethylammonium trimesate hydrate (**H6**) we have characterised structurally and energetically the strength of interactions between the anionic and cationic sublattices, which were representative of supramolecular synthons. Here again a traditional structure refinement of ethylammonium trimesate hydrate, based on a spherical atom model, was improved by the use of MAM method (**H2**). For the final multipolar model the residual factor, R(F), was improved by ca. 45%, the average B factor was decreased from 2.584 to 2.380, and the rigid-bond test (Hirshfeld, 1976) showed improvement by 49% for the final model.

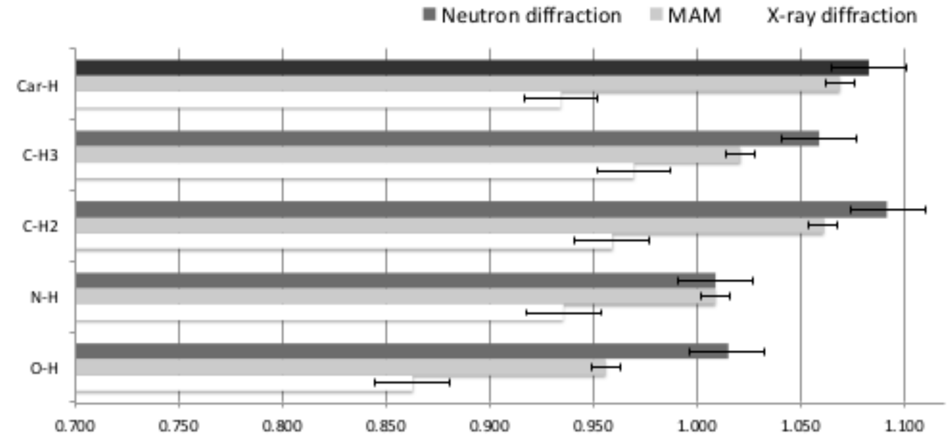


Figure 2. Average values of X–H distances in the structure of ethylammonium trimesate hydrate. White column values were obtained from the spherical refinement; grey columns values obtained from the MAM refinement. The black columns refer to average values obtained from neutron diffraction (Allen *et al.,* 1992). Error bars are indicated for all values.

Moreover, when hydrogen bonds are investigated, the geometry of the X-H bond has been improved upon the multipolar atom model refinement. First, the method allowed me to refine the hydrogen atoms positions freely with no restraints. Second, the X-H distances for the multipolar atom model were improved as judged by comparison to the average values obtained from neutron diffraction (Fig. 2). In the **H6** structure we have revealed the presence of four supramolecular synthons, two zero-dimensional synthons (S1 and S2), belonging to R_2^2 and R_4^4 graph sets, and two one-dimentional synthons (S3 and S4 chains) belonging to R_2^3 graph set. The use of the MAM method allowed me to calculate the cumulative estimated dissociation energy (eCDE) of the synthons from the following equation:

$$D_e = \frac{-a_0^3 \cdot V^{CP}}{2}$$

where a_0 is the Bohr radius and V^{CP} is the value of the potential energy at the CP (Espinosa and Molins, 2000).

As noted for halogen-based synthons (Brezgunova *et al.,* 2012), it became apparent that the eCDE values may be of use to categorize the packing motifs of importance to self-assembly. For example, synthons may be considered as primary units (secondary, tertiary, etc.) with respect to the assembly process. In other words, motifs with a higher eCDE should be more robust and favoured in the self-assembly process and ultimately in the solid state as well. Indeed, searching the Cambridge Structural Database (CSD) (Groom *et al.,* 2016) has revealed that the number of synthon occurrences for motifs S1–S4 follows the same trend as the eCDEs. The S1 synthon (highest eCDE value of 194.14 kJ·mol^{-1}) occurs in 851 structures, while S2 (eCDE = 125.26 kJ·mol^{-1}) appears in only 8 unique entries (18 entries in the hit list). In case of S3 and S4 synthons, S3 occurs in 736 structures (eCDE = 188.42 kJ·mol^{-1}) and S4 in 34 (eCDE = 164.34 kJ·mol^{-1}). The correlation between eCDE and the number of occurrences in the CSD is further justification of the suitability of the MAM approach. Moreover, the eCDE values indicate that the small S1 (R_2^2 graph set) motif is the most stable and once formed as a stand-alone structure, may direct the self-assembly process. Further characterization of the interactions in this system by means of gas-phase reaction coordinate mapping and solution studies ought to prove useful in terms of judging the proposed hypothesis and the usefulness of the proposed self-assembly mechanisms deduced by the estimated cumulative dissociation energies of packing motifs.

2. Studies of chemical properties with charge density distribution

The studies of the charge density distribution in molecules are highly important as it provides an opportunity to understand the specificity of chemical properties from a physical observable. Electron density at the subatomic level can now be observed for small-molecule crystals studied at ultrahigh resolution, mainly owing to the state-of-the-art instrumentation available to contemporary crystallographers. In contrast, for larger molecules, electron densities can be modeled at lower resolution through the application of electron-density transferability principles (Muzet *et al.,* 2003; Guillot *et al.,* 2008; Dominiak *et al.,* 2009; Johnas *et al.,* 2009). In this method, the electron-density parameters studied from small molecules are stored in the ELMAM2 database of multipolar atoms (Domagała *et al.,* 2011, 2012). Upon database transfer, chemical atom types are identified and their electron-density parameters are retrieved. In publication **H3** I applied this method for the macromolecule Cholesterol oxidase (ChOx), which is a 55 kDa secreted bacterial enzyme that binds the flavin adenine dinucleotide (FAD) cofactor (Vrielink and Ghisla, 2009). The transferability allowed me to study the electrostatic potential of the active site and to investigate the interactions between the protein and the ligand. The results show that the active site of the ChOx protein has an overall positive electrostatic potential, which is complemented by an overall negative electrostatic potential of the cofactor. The total charge on the selected protein region was found to complement the charge on the FAD molecule.

From the topological analysis of FAD-protein binding forces I found 66 intermolecular interactions in total. The numerous hydrogen bonds found between the ligand and the protein were in agreement with the specificity of this class of proteins for the FAD cofactor. The evaluation of their estimated dissociation energies derived from charge density analysis allowed me to determine their role in binding:

(i) the strongest ones are involved in the anchoring of the FAD molecule;

(ii) H-bonds influence the conformation of the FAD molecule in the active site;

(iii) interactions formed between the protein and the isoalloxazine three-ring system play a crucial role in the redox chemistry of the enzyme.

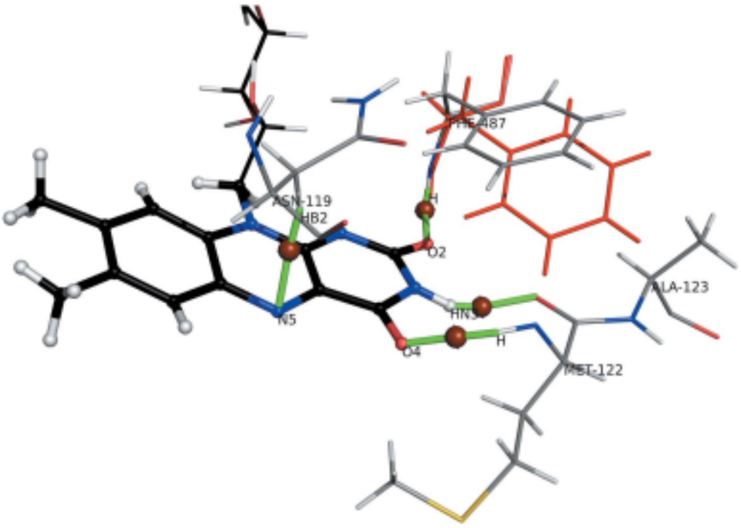


Figure 3. Residues forming the strongest intermolecular interactions with the FAD isoalloxazine moiety. The CPs are shown as brown spheres and the bond paths are shown in green.

The cofactor is involved in four strong hydrogen bonds: to asparagine (one hydrogen bond), methionine (two hydrogen bonds) and phenylalanine (one hydrogen bond) (Fig. 3). The first, an aliphatic hydrogen bond is essential, as it binds the nitrogen atom of the isoalloxazine moiety, which is the site of electron transfer to the cofactor during the redox reaction. The latter three bonds appear to influence the deformation of the moiety from its planar conformation.

It is very rare for a protein, especially of around 500 residues, to diffract to subatomic resolution, although with the improvement in data-collection, processing and refinement methods, such structures are becoming more feasible. Despite these ultrahigh-resolution structures, it is still a significant challenge to study the electrostatic and stereochemical properties of proteins. However, these challenges can be overcome, in part, by using the transferability principle.

As pointed out above, the deconvolution of experimental aspherical charge density necessitates a number of conditions to be fulfilled for high-accuracy diffraction data. The studies require measurements of reflections to high order in an acceptable period of time, however care must be taken in the choice and use of radiation source, detector, cryogenics and experimental data handling (Zhurov *et al.,* 2008). Studies presented in publications **H4** and **H5** are devoted to small molecule structures and were carried out during my one-year post-doc position at the University of Toledo in the group of prof. A. Alan Pinkerton. The group of prof. A. Alan Pinkerton is internationally recognised because of their contributions to experimental methods development and optimisation in the field of charge density analyses. The laboratory equipment is optimized for obtaining the best possible charge density data in the shortest time. The instrumentation consists of: Mo 18 kW ULTRAX-18 rotating anode generator, quarter circle goniostat, curved image plate (RAPID II, Radius 127.4 mm, active area 465 / 256 mm, 2θ from -60° to 144° and open flow He cryostat (home design, modified ESP cryosystem, min. temp 14 K). Moreover, integration of experimental data is performed by the use of dedicated software, assembled by dr Vladimir Zhurov, the member of the group.

The group of prof. A. Alan Pinkerton has developed a research program to examine the experimental and theoretical electron density distribution and the properties derived from its topology for known explosives and propellants. In particular, it has been hypothesized that shock sensitivity of energetic materials may be related to the energy of intermolecular interactions (Zhurova *et al.,* 2006). During my stay at the lab I participated in the study of the possibly most shock insensitive energetic material known *i.e.* the 1,3,5-Triamino-2,4,6- trinitrobenzene (TATB) (**H4**). The material has a very high value of impact sensitivity drop height (h_{50} = 490cm) (Rice and Hare, 2002) but possesses a rather typical velocity of detonation for organic explosives (VOD = 7350 m/s) (Cooper, 1996). The structure of the molecule is well known. It has been studied both experimentally (Cady and Larson, 1965) and theoretically in the gas phase (Stephen *et al.,* 2011) and solid-state (Zhang et al., 2014). The studies indicate unusual bond lengths in this compound. Based on the structural data, I proposed a series of canonical resonance structures, which might contribute in the mesomeric resonance hybrid (Fig. 4). The analysis of precise charge density data *i.e.* value of the electron density at the bond critical point, topological bond orders, bonds ellipticities and integrated atomic charges showed that the main resonance structure which contributes in the hybrid is structure III.

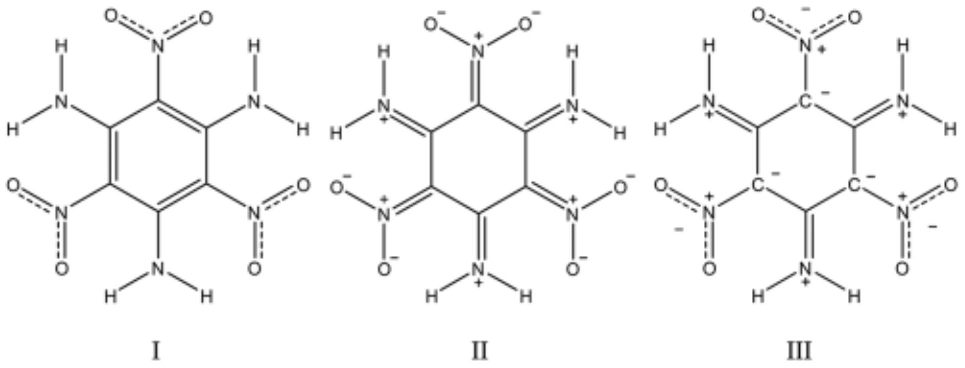


Figure 4. Canonical structures of 1,3,5-Triamino-2,4,6- trinitrobenzene.

Additionally, these studies demonstrated good agreement between experiment and theory using the experimental geometry and periodic boundary conditions, but less so with molecules or molecular pairs in the gas phase. This outcome supports my previous conclusions that transferred multipolar model parameters from a periodic solid-state theoretical calculation are more advantageous than one calculated in the gas phase.

Periodic calculations were also used in studies of 2,5-dichloro-1,4-benzoquinone (DCBQ) and its charge density analysis (**H5**). However, the use of these calculations were far more worthwhile in this case, as the studies were devoted to re-examination of incomplete analysis of the electron density (Hathwar *et al.,* 2011), where the electronegative chlorine atom covalently bonded to a carbon atom was surprisingly reported to carry a positive monopole charge. The re-examination of studies is always challenging and need to be done objectively and carefully. The results of the analysis from least-squares refinements highlighted two possible experimental models for DCBQ: Model 1, which reproduced the original positive charge of the chlorine atom, and Model 2, which resulted in a neutral chlorine when a more flexible kappa set was refined. The experimental models were also compared to a model derived from refinement against theoretical structure factors (TSF), obtained from periodic solid-state calculations and resulted in a negative monopole charge for the chlorine atom (Table 2).

Table 2.
Monopole charges for experimental multipole Models 1, 2 and TSF for DCBQ.

Atom	Model 1	Model 2	TSF
Cl1	**+0.130(10)**	**0.000(15)**	**-0.060(13)**
O1	-0.144(16)	-0.183(16)	-0.120(4)
C1	-0.068(14)	+0.055(16)	-0.028(23)
C2	+0.052(16)	+0.074(15)	+0.046(22)
C3	-0.099(18)	-0.064(18)	+0.064(22)
H1	+0.129(14)	+0.118(13)	+0.097(4)

From the statistical evaluation of the refinements, R factor, normal probability plots, and fractal plots there are only minor differences perhaps favouring Model 2. All residual maps were clean, that of Model 2 being marginally better than Model 1. From the presented results, the differences between the multipole models are subtle, however Model 2 and the TSF Model are as expected from electronegativity arguments. Nevertheless, it needs to be noted that in all cases the chlorine charge derived from the integration over Baders atomic basins is negative. In some sense it was satisfying to know that the multipolar expansion expression (Hansen and Coppens, 1978) for the electron density is sufficiently flexible to provide similar descriptions of the electron density with a somewhat different parameter set. This, however, does not suggest that multipole refinements can be carried out "automatically" without a critical examination of the results at each stage of the refinement.

Table 3.
Correlation coefficients between experimental and theoretical charge density analysis: ρ_{CB} - total charge density in BCPs of intramolecular interactions (covalent bonds); ρ_{NCB} - total charge density in BCPs of intra and intermolecular interactions (non-covalent bonds); n_{topo} topological bond orders and D_e intermolecular interactions dissociation energies.

		Correlation coefficients			
Compound	Publication	ρ_{CB}	ρ_{NCB}	n_{topo}	D_e
1-nitroindoline	H1	0,988	0,954	0,951	0,964
TATB	H4	0,963	0,913	0,996	0,999
DCBQ	H5	0,999	0,988	0,920	0,985

The common highlight from publications **H4** and **H5** is the use of periodic theoretical calculations as reference models. Similar to topological analysis of charge density of norbornene derivatives (Gianopoulos *et al.*, 2016), which was described in a publication not considered in my scientific achievement due to formal defects (no contact with one of the co-authors). The consistency of experimental and theoretical data is striking (Table 3) and further justifies use of periodic quantum-mechanic calculations in the Multipolar Atom Model approach described in **H2**.

3. Summary

The result of the research, described above through a series of six publications, provided new knowledge on charge density analysis and its use for the optimisation of molecular structures obtained from X-ray diffraction experiments and the tools to investigate properties of chemical compounds.

Charge density analysis is a universal method and can be used for both, experimental and theoretical data. Importantly, the multipolar atom model can be successfully transferred from charge density databanks or from the theoretical model refined over periodic wave functions calculations. This can be useful especially for problematic cases when ultrahigh-resolution data cannot be collected, like in case of macromolecules or when limited by the instrumentation used for measurement. These studies also indicate that the theoretical data obtained from periodic solid-state calculations can serve not only as the source of analysis but also as the reference data for experimental research as they are coherent when precise and sophisticated measurements are made. Moreover, the use of transferred data for structure optimisation brings the opportunity to simultaneously analyse more accurately all interatomic and intermolecular interactions, especially hydrogen bonds when corresponding neutron diffraction data are unavailable.

4. Perspectives

4.1. Theoretical Library of Multipolar Atom Model (TLMAM)

The proposed MAM approach provides opportunities to create a new multipolar databank *i.e.* transferable theoretical library of multipolar atom model (TLMAM) describing the precise electronic density in proteins and nucleic acids. As mentioned above, currently there are three multipolar atoms libraries developed by the charge density community: one experimental (crystallographic) built by CRM^2 ELMAM/ELMAMII (Zarychta *et al.,* 2007; Domagała *et al.,* 2011) and two libraries derived from theoretical computations: UBDB – University at Buffalo aspherical–atom DataBank (Volkov et al., 2004; Volkov & Coppens, 2004; Dominiak et al., 2007) and Invariom database (Dittrich et al., 2006).

Table 4.
The comparison of currently available multipolar parameters databanks (Johnas et al., 2008) and the library proposed in present project. Adventages in light green, disadvantages in light orange.

	Invariom database	UBDB	ELMAM/ELMAM II	TLMAM
Transferability 'cutoff'	Empirical rules	Statistics	Empirical findings/statistics	Empirical findings/statistics
Database construction	Geometry optimizations of model compounds	Single–point energy calculations of structures from the CSD	Multipole refinements of high–resolution X–ray data	Periodic geometry optimizations of structures from the CSD + Multipole refinements of theoretical high–resolution X–ray data
Method used	B3LYP, basis D95++(3df,3pd)	B3LYP, basis 6–31G*	High-resolution X–ray diffraction	Atomic resolution X–ray diffraction + B3LYP,basis 6–31G(*d*, *p*)
Main aim	Structure refinement and property calculation	Structure refinement and property calculation	Structure refinement and property calculation	Structure refinement and property calculation
Known strengths/weaknesses	Does not include effects of hydrogen bonding	Does not include effects of hydrogen bonding	Includes average effect of hydrogen bonding	Includes average effect of hydrogen bonding
	Easily extendable to new chemical environments	Easily extendable to new chemical environments	Experiment required for extension database	Easily extendable to new chemical environments
Organization	Invariom notation	No direct link between scattering factor and its name	IUPAC notation for protein atoms	IUPAC notation for protein atoms

The main difference between TLMAM and theoretical libraries is the fact that those two are based on the theoretical calculations *in vacuo*, thus they do not take into account the importance of intermolecular interactions such as hydrogen bonds. In the proposed databank, the multipolar parameters will be modeled from periodic solid-state quantum calculation, therefore the discrete deformations of charge density related to intermolecular interactions will be kept. As indicated by Mladenovic and co–workers (2009), the influence of the environment on the electron density increases in the order gas phase < polar solvent < crystal < protein (Mladenovic *et al.,* 2009). This shows that computations based on molecular structures in the crystallographic environment is a more accurate and meaningful approach than that derived from *in vacuo* calculations. It seems to be a perfect addendum of the state–of–the–art experimental and theoretical multipolar parameters libraries. The database will not suffer from inaccuracy introduced by poorly measured high-resolution X–ray diffraction intensities and other systematic errors as compared to the purely experimental library. The comparison of the abovementioned approaches is listed in Table 4. From this perspective it is clear that

TLMAM database will merge the advantages of the currently available libraries of multipolar atom models while also addressing some of their disadvantages.

4.2. Self-assembly mechanism investigation

As described in **H6** publication, the use of the MAM method brings opportunities to study the self-assembly mechanism. Dissociation energies of supramolecular synthons of organic salts is under investigation. To date we have already synthetized over 30 structures in our laboratory composed of different carboxylic acids and amines. Our preliminary studies of the synthons assemblies have revealed a number of unique connections between ions in the structures. I believe that further investigations of intermolecular interactions by means of charge density analysis derived from the MAM approach will allow us to construct more general conclusions in the self-assembly mechanism relevant to structures observed in the solid-state.

4.3. Energetic compounds investigations

Another project underway is an investigation of the molecular, crystal and electronic structure of new aliphatic and aromatic energetic compounds, as well as their interactions at the electronic level by means of the MAM method. Results should provide new knowledge of the energetic compounds properties and chemistry and also of their derivatives in the solid state and the gas phase. The studies will allow finding the relationships between the structures of compounds and the geometry of intra- and intermolecular interactions in crystals.

4.4. MAM approach advancement

Without any doubt the MAM approach itself can be still developed further. I plan to implement automatic protocols, where new, in-house developed computer programs or graphical shells can be employed to easily implement the method. The theoretical calculations can be optimised in terms of using a different parameter hybrid density functional or/and how molecule or cell parameters are optimised or if the molecule actually should be optimised in cases when neutron diffraction experiments are available. The HAR method (Capelli et al., 2014) briefly described above further encourages modifying and refining the MAM approach. For example, simply adding an additional step in the procedure *i.e.* refinement of the model in cycles of structure refinement - resulting in molecular optimisation of the electron density distribution in response to adjustments or small changes in molecular geometry.

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D) Presentation of other scientific achievements

My scientific interests and activities so far have focused on charge density anlysis and structural characterisation of organic and mixed organic-inorganic structures.

In June 2008 I took a PhD degree with honours in crystal chemistry at the Institute of Chemistry, University in Opole, Poland. The Ph.D. thesis was devoted to the synthesis, crystal structures and phase transitions of halogenoantimonates(III) and bismuthates(III). Halogenoantimonates(III) and halogenobismuthates(III) of the general formula $R_aM_bX_c$ (where R is an organic cation; M is Sb or Bi and X is Cl, Br or I) are very interesting groups due to the polar properties of a number of compounds.

Nevertheless, my research is mainly focused on bridging our knowledge regarding the macroscopic properties of matter and the versatile functionality of molecules with their internal, electronic and structural characteristics. The research involves theoretical and experimental tools and methods from computational chemistry to advance practical aspects of modern crystallography. In 2004 I was honored with the scholarship of French Government for a research project in the Laboratory of Prof. Claude Lecomte at University of Henri Poincaré in Nancy, France. This project has developed into a long-term collaboration with their laboratory. Visit in the laboratory and discussions with coworkers (including prof. Niels Hansen) made me fascinated in charge density studies as well as macromolecular crystallography. In 2006 I was highly involved for nine months in a project funded at CRM^2 by the French Agence Nationale de la Recherche (LibrarEnergy, 2005-2008). The project was to build and implement a library of average multipole populations describing the electron density of chemical groups in all 20 amino acids found in proteins. The library values were obtained from several small peptide or amino acid crystal structures refined against ultra–high–resolution X–ray diffraction data. The library transfer was extremely successful and yielded accurate electrostatic potentials. The outcome has been published in Acta Crystallographica Section A.

Between 2009 and 2014 I visited the CRM^2 laboratory of CNRS-Institut Jean Barriol, University of Lorraine (Vandoeuvre-lès-Nancy, France) several times as visiting professor. During my stays I acquired the necessary experiences to capitalize in the field of charge density analysis, transferability of multipolar atom models and fusion between theoretical calculations and experimental structural data. Moreover I participated in the series of lectures of prof. George T. DeTitta, State University of New York at Buffalo, U.S.A., in the field of biological macromolecules crystallization. The cooperation with prof. Christian Jelsch (Director of Research) resulted in two major publications which are included in my scientific achievements discussed previously.

In 2015 I was chosen for a one-year post-doctoral position at the Department of Chemistry and Biology at The University of Toledo (Ohio, USA) to work in the group of prof. A. Alan Pinkerton. I gained further experience in charge density studies carrying out sophisticated low-temperature, ultrahigh-resolution X-ray diffraction experiments. A significant part of my research contributions during my stay consisted of four scientific publications in journals included in the JCR database. Two of them are included in my scientific achievements discussed above.

After my Ph.D. I was also involved in other scientific projects:

(i) Rational design of new materials with tailored properties and predictable structural trends in crystals composed of salts of carboxylic acids and amines. The project relies on the MAM approach, which is included in my present scientific achievements. Project is under investigation.

(ii) Structural characterization of polar metal-formate and bimetallic frameworks in collaboration with scientists from Institute of Low Temperature and Structure Research Polish Academy of Sciences (Wrocław, Poland). The project already resulted in two publications: Ptak, M., Zarychta, B., Stefańska, D., Ciupa, A., Paraguassu W. Dalton Trans. 2019, 48, 242–252; Trzebiatowska, M., Zarychta, B., Pikul, A., Mączka, M., Peksa, P., Poprawski, R., PhyChemChemPhys. 2017, 19, 16749-16757. Project is under investigation.

(iii) Design and synthesis of perovskite-like dielectric crystals based on mixed organic-inorganic polymers. The project is granted financial support from the National Science Centre (2018/02/X/ST3/00483 MINIATURA 2) to dr. Magdalena Rok from Wrocław University (Poland). The project already resulted in one publication: Rok, M., Bator, G., Zarychta, B., Dziuk, B., Repeć, J.,Medycki, W., Zamponi, Usevičius, G., Šimėnas, M., Banys, J., Dalton Transactions - DT-ART-12-2018-005082, accepted. Project is under investigation.

(iv) Synthesis and characterization of Cu(II) compounds and complexes in terms of its structural properties (Olijnyk, V., Zarychta, B. J. Mol. Struct. 2016, 1106, 259-264); as hardener for epoxy resins (Lavrenyuk, H., Mykhalichko, O., Zarychta, B., Oliynyk,V., Mykhalichko, B. J. Coord. Chem. 2016, 69, 2666–2676); fire retardant (Mykhalichko, O., Lavrenyuk, H., Zarychta, B., Oliynyk V, Mykhalichko B. J. Mol. Struct. 2015, 1095, 34-41) or its crucial role in redox systems (Olijnyk, V., Zarychta, B., Kinzhybalo, V. Polyhedron 2014, 69, 234–239).

E) Summary of scientific achievements

I am the co-author of 70 scientific publications (including 14 structural reports), of which 47 publications are in journals included in the Journal Citation Reports (JCR). The total impact factor (IF) is 81.605. The total number of citations of these publications, excluding self-citations according the Web of Science is 245, and h-index = 7.

	Pre-doctoral	Post-doctoral	Total
Publications			
Amount of JCR publications	15	32	**47**
Amount of other publications	8	1	**9**
Structural reports		14	**14**
Citations	163 (153)*	101 (92)	**264 (245)**
Impact Factor	11,328	70,277	**81,605**
MNiSW points**	255	815	**1070**
Conferences			
Lectures	3	2	**5**
Announcements and posters	8	3	**11**
Lecture invitations (non-conference)	0	2	**2**
h-index			**7**

* data in brackets are values without autocytations.

** for publications published before 2011, points are taken from 2011/2012 MNiSW list.