FACULTY OF
CHEMISTRY
University of Lodz

Author's review on her research

(Annex 2b)

Agnieszka J. Rybarczyk-Pirek

Faculty of Chemistry UL , Department of Theoretical and Structural Chemistry
91-403 Lodz, Tamka 12, www.chemia.uni.lodz.pl

1. First name and surname

Agnieszka Joanna Rybarczyk-Pirek

2. Obtained diplomas nad scientific degrees

- June 1996 – M.Sc. in chemistry, Faculty of Physics and Chemistry, University of Lodz

Title of M.Sc. thesis: "Determination of crystal structure of 6,7-dihydroxy-1-(methoxyphenyl)-1,2,3,4-tetraisoquinoline hydrochloride by X-ray diffraction methods"
Thesis supervisor: Dr. Tomasz Olszak (Ph.D.), University of Lodz
Reviewer: Professor Dr. hab. Mieczysław Grabowski, University of Lodz

- March 2006 – – Ph.D. in chemical sciences, Faculty of Physics and Chemistry, University of Lodz

Title of Ph.D. thesis: "The analysis of intra- and intermolecular interactions in crystalline state based on X-ray diffraction analysis of chromone and coumarin phosphoryl derivatives"
Thesis supervisor: Prof. Dr. hab. Sławomir Grabowski, University of Lodz
Reviewers: Prof. Dr. hab. Henryk Piekarski, University of Lodz;
Prof. Dr. hab. Zofia Kosturkiewicz, Adam Mickiewicz University in Poznan

3. Employement in scientific institutions

- 1996 - 1998 – employed on the post of Senior Chemist Officer, Department of Crystallography, Faculty of Physics and Chemistry, University of Lodz
- 1998 - 2006 – employed on the post of Assistant, Department of Crystallography, Faculty of Physics and Chemistry, University of Lodz
- 2006 until present – employed on the post of Assistant Professor, Department of Theoretical and Structural Chemistry, Faculty of Chemistry, University of Lodz

4. Presentation of scientific achievements according to Article 16 section 2 of Act of law as of March 14, 2003 about scientific degrees and scientific title and about scientific degrees and scientific title in art [Dz. U. 2016 r. p. 882 with changes in Dz. U. from 2016 p. 1311]:

4.1. Title of the scientific achievement

"From hydrogen bonds to halogen bonds – the analysis and characteristics of selected stabilizing intermolecular interactions in the crystalline state"

4.2. List of publications:

(corresponding author presented with symbol ”*”).

[H1]. Elżbieta Bilewicz, **Agnieszka J. Rybarczyk-Pirek**, Alina T. Dubis, Sławomir J. Grabowski*
"Halogen bonding in crystal structure of 1-methylpyrol-2-yl-trichloromethyl ketone" –
Journal of Molecular Structure (2007), 829, 208-211; DOI: 10.1016/j.molstruc.2006.06.032

[H2]. **Agnieszka J. Rybarczyk-Pirek***
"Co-crystal / salt crystal structure disorder of trichloroacetic acid – *N*-methylurea complex with double system of homo- and heteronuclear O-H...O / N-H...O hydrogen bonds - X-ray investigation, *ab initio* and DFT studies"
Structural Chemistry (2012), 23, 1739-1749; DOI: 10.1007/s11224-012-9980-7

[H3]. **Agnieszka J. Rybarczyk-Pirek***, Lilianna Chęcińska, Magdalena Małecka, Sławomir Wojtulewski
"Intermolecular interactions of trichloromethyl group in the crystal state, the case of 2-trichloromethyl-3*H*-4-quinazoline polymorphs and 1-methyl-2-trichloroacetylpyrrole - Hirshfeld surface analysis of chlorine halogen bonding"
Crystal Growth & Design (2013), 13, 3913-3924; DOI: 10.1021/cg400584w

[H4]. **Agnieszka J. Rybarczyk-Pirek***, Marlena Łukomska, Krzysztof Ejsmont, Marcin Jasiński, Marcin Palusiak
"Temperature-dependent polymorphism of *N*-(4-fluorophenyl)-1,5-dimethyl-1H-imidazole-4-carboxamide 3-oxide: experimental and theoretical studies on intermolecular interactions in the crystal state"
Structural Chemistry (2014), 25, 979-989; DOI: 10.1007/s11224-014-0404-8

[H5]. Marlena Łukomska, **Agnieszka J. Rybarczyk-Pirek**, Mirosław Jabłoński, Marcin Palusiak*
"On the nature of NO-bonding in *N*-oxide group"
Physical Chemistry Chemical Physics (2015), 17, 16375-16387; DOI: 10.1039/c5cp02148k

[H6]. **Agnieszka J. Rybarczyk-Pirek***, Marlena Łukomska-Rogala, Sławomir Wojtulewski, Marcin Palusiak
"*N*-oxide as a proton accepting group in multicomponent crystals: X-ray and theoretical studies on new *p*-nitropyridine-*N*-oxide co-crystals"
Crystal Growth & Design (2015), 15, 5902-5813; DOI: 10.1021/acs.cgd.5b01177

[H7]. **Agnieszka J. Rybarczyk-Pirek***, Magdalena Małecka, Marcin Palusiak
"Use of Quantum Theory of Atoms in Molecules in the search of appropriate hydrogen atom locations in X-ray diffraction based studies"
Crystal Growth & Design (2016), 16, 6841-6848; DOI: 10.1021/acs.cgd.6b00943
This publication was awarded by the Journal by being presented on the front cover of issue No. 12 of the relevant year of edition

[H8]. Marlena Łukomska-Rogala, **Agnieszka J. Rybarczyk-Pirek***, Krzysztof Ejsmont, Marcin Jasiński, Marcin Palusiak
"Non-covalent interactions of *N*-phenyl-1,5-dimethyl-1*H*-imidazole-4-carboxamide 3-oxide derivatives – the case of intramolecular *N*-oxide hydrogen bonds"
Structural Chemistry (2017); 28, 1229-1241, DOI: 10.1007/s11224-017-0935-x

4.3. Presentation of scientific aim of the above publications, the obtained results and their possible application.

Introduction

The 20th century in crystallography can be called the age of intramolecular structural chemistry. The chief aim of the performed investigations was to get well acquainted with the spatial structure of various groups of chemical compounds. This large-scale undertaking which was continued for many years, resulted in reinforcing the contemporary knowledge of the structure of molecules of almost all chemical bonds.

In the last few years the point of interest of crystallography was shifted from a detailed analysis of molecular structures to studying the ways of their associations. The associated molecules form larger complexes which are stabilized by various interactions. Most frequently these are hydrogen bonds, donor acceptor bonds, $\pi \ldots \pi$ interactions or dispersion forces. Such interactions are generally much weaker than covalent bonds, so the intermolecular structures can easily form or disintegrate.

Molecular association is a common phenomenon in nature. Because of its importance for biochemical processes multiple investigations were carried out aiming to find out more information about the processes affecting self-assembly of the molecules. In this context the identification and description of intermolecular forces should be treated as the initial stage of learning about the rules that govern self-assembly of the molecules. That is why the problems connected with stable molecular interactions have become one of the main subjects in present-day crystallography.

My research interests developed in a way similar to that presented above. Ever since I started to work on my M.Sc. thesis my research activity has been focused on crystallography. The aim of my investigations has been to obtain thorough knowledge of the structure of molecules and crystals of various organic, metal-organic or complex compounds. This cognitive aspect of my research work has not changed until today.

However, the description of the structure of a crystal does not mean only the description of its molecular structure, but also the analysis of how the molecules are distributed in the crystal lattice. It often happens that the architecture of crystals of very similar compounds differs significantly. The questions then arise as concerns the observed differences. We keep asking ourselves why the molecules of some compounds form a certain type of aggregates, while the molecules of other compounds form completely different aggregates. We then start searching for significant intermolecular interactions and relate their presence to the architecture of crystals. We attempt to answer a question how significant is the influence of different intermolecular forces on the ways of molecular packing in the crystalline state and on the stability of the structure formed. Questions of this kind appear over and over again while we identify a new crystal structure. It is because of these questions that my research interests began to concentrate more on problems related to intermolecular interactions and their impact on the architecture of crystals.

My Ph.D. thesis was concerned both with the description of the molecular structure of chromone and coumarin derivatives, as well as the way of their packing and intermolecular interactions in the crystals. The latter aspect of studies, connected with the analysis and identification of non-covalent intermolecular interactions, has become the main subject of my later publications. From the point of view of a crystallographer, I consider this subject to be very interesting while not yet fully known and explained.

The subject, aim and range of studies

The importance of molecular associations in many biological processes [1-2] has become one of the reasons why multiple studies were undertaken on various types of molecular interactions. At present, while designing new molecular complexes, researchers make use of highly direction- specific intermolecular interactions, among them first of all hydrogen bonds. An increased interest is also focused on interactions characterized by lower energies, such as the π...π interactions or halogen bonds. These types of intermolecular interactions have also become the main subject of my investigations.

In this author's review, as the basis of my scientific achievement I present the results of investigations into hydrogen bonds and halogen bonds in the group of crystals of organic compounds. The common feature of the examined organic compounds is that they are all molecular crystals. The multicomponent crystals (known also as solid solutions) constitute an interesting group among the examined compounds. In the further part of the Author's review they will be called co-crystals [3, 4-8].

Different structures of molecules of the examined chemical compounds, as well as of their functional groups, supplied me with a vast amount of information to analyze the role which is played by intermolecular interactions in stabilization of the crystal structure. The investigations included several different projects taking into account various specific problems. In the majority of cases a hydrogen bond was the starting point, including the effect of strong interactions of this kind on the structure of a crystal. My investigations were also focused on the analysis of halogen bond crystal structures.

The chief aim of my studies was to establish the crystal structure of the examined groups of compounds as well as to describe the character and the role played by intermolecular interactions as indicated in the title. In order to achieve that aim, I used both the experimental and theoretical methods. I determined the crystal structure of the examined compounds on the basis of crystal diffraction studies. The use of calculation methods of modern quantum chemistry, and in particular Quantum Theory of Atoms in Molecules (QTAIM) [9] and Natural Bond Orbitals (NBO) [10] allowed me to expand the scope of the performed investigations so as to include the elements describing the energy characteristics of the analyzed systems. In addition, in order to compare intermolecular interactions observed in the crystalline state, I used the Hirshfeld Surface (HS) analysis [11]. When describing the obtained results, I used the commonly known geometry and energy criteria so as to facilitate their comparison with other similar systems.

In the present author's review the obtained results are presented according to the order in which individual consecutive problems were examined in my publications.

Intramolecular hydrogen bonds in *N*-oxide derivatives

There are many types of intermolecular interactions that decide about the distribution of the molecules in crystals. Among them there is a hydrogen bond which arouses continuous interest of the chemists [2-14].

As a highly direction-specific interaction, the hydrogen bond is often considered to be one of the most important interactions responsible for the distribution of molecules in molecular crystals. The hydrogen bond is formed when the donor group (D-H) approaches the atom acceptor (A) which is characterized by possessing a lone electron pair at a distance close to the sum of van der Waals radii. That is why this interaction is usually denoted as D-H...A. In the classical sense, the D and A atoms denoted the atoms of the elements characterized by high electronegativity. At present it is assumed that carbon atoms and even π electrons can behave as the acceptor centers [15].

Hydrogen bonds are characterized by energy values ranging from 0.2 to 40 kcal/mol [16]. This energy is significant enough to make possible the formation of stable molecular complexes. Among strong interactions of this type should be mentioned the charge-assisted hydrogen bonds (CAHBs(+),CAHBs(-) and CAHBs(+/-)) and the resonance assisted hydrogen bonds (RAHBs) [17-19] to which partly covalent character is ascribed as being the result of negative charge flow from the acceptor to the donor [20-21].

Among strong hydrogen bonds there are also the low barrier hydrogen bonds (LBHBs) in which the reaction of proton transfer can proceed and which also arouse much interest [22]. They are characterized by high energy values and short *d*(D...A) distances. Sometimes they are called the short strong hydrogen bonds

(SSHBs) [23]. It is assumed that the LBHBs appear when the distance between the donor and acceptor atoms is less than 2.55 Å for homonuclear interactions O-H...O and 2.65 Å for heteronuclear interactions N-H...O [24], whereas their energy can attain a value of over 30 kcal/mol.

In the context of studies on strong hydrogen bonds my attention was focused on interactions of the *N*-oxide group as the proton acceptor in crystal structures of the derivatives of imidazole *N*-oxide (*N*-phenyl-1,5-dimethyl-1*H*-imidazole-4-carboxamide 3-oxide). These investigations were a natural continuation of my earlier studies concerning intramolecular hydrogen bonds, which I carried out in connection with my Ph.D. thesis.

A series of derivatives of imidazole *N*-oxide aroused my interest because of interesting spectral results [25]. The results of NMR investigations suggested the presence of a rather strong hydrogen bond with participation of the carboxamide group as a donor. Crystallographic studies unequivocally confirmed the presence of an intramolecular hydrogen bridge to the *N*-oxide group [**H4**, **H8**] (Figure 1) which was accompanied by internal chelate ring closing *S(6)* [26]. Interactions of this type belong to a group of heteronuclear resonance assisted hydrogen bonds (RAHBs). They are usually weaker than the homonuclear bonds [27-28] because of large differences in proton affinity between the donor and acceptor atoms, but they can be strengthened by introducing the substituents that are able to reduce the differences.

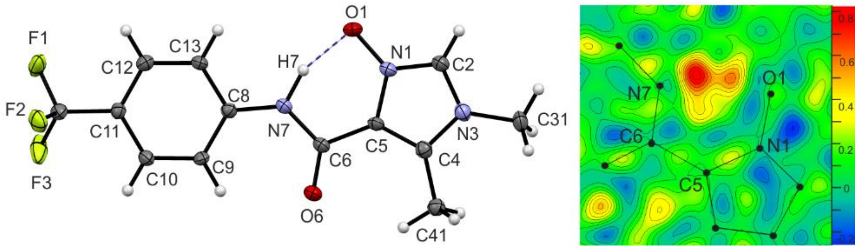


Figure 1. The structure of N-(4-trifluoromethylphenyl)-1,5-dimethyl-1H-imidazole-4-carboxamide 3-oxide with an intramolecular hydrogen bond N-H...ON (on the left, dashed line); the difference Fourier map in the area of an intramolecular hydrogen bond (on the right), electron density values are presented by color scale and the contour map (change of contour by every 0.1 $eÅ^{-3}$*). The map was calculated for a model without the hydrogen atom.*

The difference Fourier maps in the analyzed areas of hydrogen bonds, in particular for the derivatives with highly electronegative substituents in the *para* position of the phenyl ring, show a broadening or a shift of hydrogen atom maximum towards the acceptor hydrogen bond. The presented figure of the trifluoromethyl derivative suggests that there are two possible locations of the hydrogen atom and shows that a proton transfer may occur in the hydrogen bridge. The geometry parameters of the analyzed interactions show that in the examined group of crystals there exist strong hydrogen bonds (SSHBs) with the donor-acceptor distances d(N...O) of the order 2.59 – 2.71 Å and angle values <(N-H...O) in the range of 145 – 160 °.

The convergence of geometry parameters, both those obtained by X-ray studies and those obtained on the basis of geometry optimization of the molecules (B3LYP/6-311++G**) confirms that the analyzed hydrogen interactions can be strengthened or weakened by the mesomeric effect. The substituents in the *para* position of the phenyl ring significantly affect the proton donor properties of the amide group. For instance, the highly proton accepting groups cause a strengthening of the hydrogen bond whereas the weakest hydrogen bond appears for the unsubstituted derivative.

The performed investigations allowed me to conclude that the oxygen atom of the *N*-oxide group is a good acceptor of heteronuclear hydrogen bonds. In the examined crystal structures some relatively short hydrogen bridges are formed that stabilize the structure of the molecule and make the rotations around single bonds impossible. The obtained results also show that when the substituents in the examined systems are chosen appropriately then a significant energy modification of the hydrogen bond is possible that leads to the reaction of proton transfer between the donor group and the acceptor group.

The structure of *N*-oxide group

The described results of structural studies of imidazole derivatives drew my attention to the fact that it might be possible to use the *N*-oxide group to design and stabilize new crystal structures. A review of literature data showed that neither the structure nor the properties of this group are yet fully known, so it seemed important to me to get a closer insight into the problem.

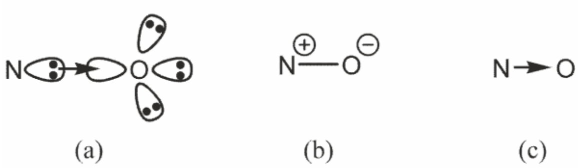


Figure 2. A schematic diagram of N-oxide bond: Lewis structure with the schematically presented locations of lone electron pairs of nitrogen atoms and the oxide (a); structural formula showing formal charges (b); structural formula showing the coordination character of N-oxide bond (c).

From the classical point of view, the *N*-oxide group bond is usually presented as a single coordination bond or by introducing atomic formal charges (Figure 2). However, the distances between nitrogen atoms and oxygen atoms or the frequencies of stretching vibrations are closer to the values characteristic of double bonds. On the other hand, a bond of double character would violate the octet rule, hence in the literature there are several concepts that explain the properties of the *N*-oxide bond.

According to the packing model [32], the fact that the nitrogen atom forms bonds to maximally four different vicinal atoms results from its size and steric availability and not from the octet rule. The weakening and lengthening of some bonds to the *N*-oxide nitrogen atom would result in the strengthening and shortening of other bonds while retaining the total number of bonds. That is why it was suggested that the observed strong and short nitrogen-oxygen bond should be presented as a double bond in spite of a violation of the octet rule.

In order to retain the octet rule while describing the *N*-oxide bond, other publications refer to the interaction of lone electron pairs of the oxygen atom with antibonding orbitals as a stabilizing effect. The mentioned electron interactions are known as the hyperconjugation, when there is electron density transfer from lone electron pairs of the oxygen atom to the σ^* orbitals (LP(O)$\rightarrow\sigma^*$) [33-34] or the π donation (LP(O)$\rightarrow\pi^*$) [35], when the orbitals of π^*-type are concerned. The latter effect, which is also called the π-backbonding bond formation, in some cases would even afford the nitrogen-oxygen bond having triple character.

The reports based on topological analysis show that there occurs electron density transfer from the nitrogen atom to the oxygen atom, which is in agreement with the description of the *N*-oxide bond as being highly polar [36]. However, the presence of three extreme values of the Laplacian of electron density within the oxygen atomic basin of alternating orientation to *N* bonds, which is interpreted as the presence of three electron pairs, contradicts both the concept of hyperconjugation and of the π donation. According to the authors, the strengthening of the *N*-oxide bond would be the result of electrostatic interactions only, while the bond itself should be interpreted as a single highly polar bond.

It should be emphasized that the hitherto-performed investigations were focused on the derivatives of aliphatic amines. However, I decided to draw my attention to aromatic *N*-oxides as they are important owing to a wide range of application possibilities (as synthetic intermediate compounds, oxidizing materials, ligands, or precursors of active substances) [37]. In the first place, imidazole *N*-oxides were chosen as the object of my investigations, having in mind the results described in the previous part. However, among the *N*-heterocyclic compounds the derivatives of six-membered aromatic systems also occurred to be very interesting. These compounds can be treated as fundamental building bricks of the pyrimidine and purine amines, while in their molecules one can expect a significant influence of π electron effects on the nature of *N*-oxide bond and on its proton acceptor properties.

In order to better know and describe the nature of the *N*-oxide group in the above-mentioned aromatic compounds the quantum chemistry calculation methods were used (B3LYP/aug-cc-pVTZ) [**H5**]. The aim of the performed calculations was to optimize the structure and topological analysis of electron density (QTAIM) of selected model compounds. For comparison the derivatives of ammonia *N*-oxide were also taken into account in which the nitrogen atom is ascribed formal sp^3 hybridization, similarly as in the case of *N*-oxides of aliphatic amines.

In the case of the derivatives of imines, imidazole and pyridine the obtained values of electron density of the critical point of the nitrogen-oxygen bond ρ_{BCP}(NO) (0.42 – 0.45 a.u.) and the delocalization index DI(NO) (1.49 – 1.56 a.u.) are clearly higher than those obtained for a single bond in the hydroxyamine molecule (ρ_{BCP}(NO) = 0.28 a.u. and DI(NO) = 1.24 a.u., respectively). The ellipticity values of the *N*-oxide bond, changing from 0.61 to 0.75 indicate that the π donation is an essential stabilizing agent. Good correlation between bond energy and bond ellipticity (correlation coefficient R = 0.983) shows that the stabilization or destabilization of the *N*-oxide bond are above all the result of its π character (participation of π donation).

Another evidence of partly double character of the *N*-oxide bond in the examined aromatic compounds is the picture of two extreme values of electron density concentration (Figure 3), localized symmetrically in the ring plane. It shows the presence of two lone electron groups similarly as in the carbonyl group.

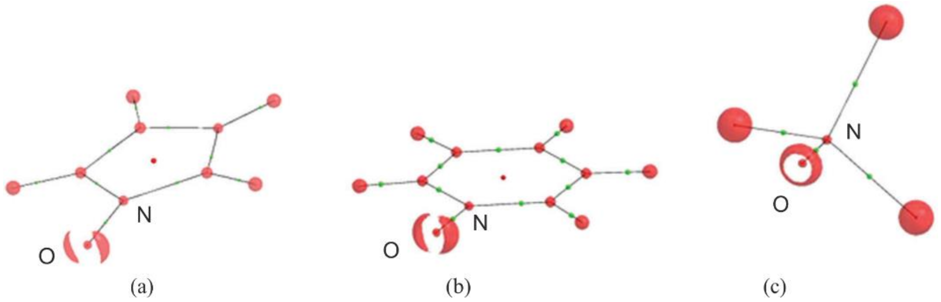


Figure 3. Graphical representation of the vicinity of N-oxide bond. The appropriate Laplacian iso surface of electron density is presented to show the location of lone electron pairs of the N-oxide group oxygen atom.

The performed investigations were supplemented by the analysis of natural bond orbitals (NBO). The Natural Resonance Theory (NRT) was applied which, while taking into account the delocalization of electrons, permitted the assessment of contribution of different resonance structures and lone electron pairs.

In the examined derivatives of aromatic *N*-oxides the partly double bond character is shown by an increase of the number of nitrogen-oxygen bonds as compared with a typical single bond (from 1.20 to 1.35) and a decrease of the average number of lone electron pairs of the oxygen atom from 3 to about 2.6–2.7. Both these tendencies result from an increased contribution of resonance structures with a double bond, which confirms that partly double character of the *N*-oxide bond is due to π donation.

The presented results show that the nitrogen-oxygen bond in *N*-oxides of the examined aromatic systems is of intermediate character between a single bond and a double bond. It gets strengthened as a result of electron density transfer from the orbitals of lone electron pairs of the oxygen atom to the antibonding type π* orbitals of nitrogen-carbon bonds. They also provide a suggestion why the π electron effects (e.g. mesomeric effect) can significantly affect the *N*-oxide bond properties. This was confirmed by the studies performed for pyridine *N*-oxide derivatives. The introduction of substituents in the *para* position of the aromatic system clearly affects the character of the nitrogen-oxygen bond. The nitro group stabilizes, strengthens and shortens it, whereas the amino group has the opposite effect. Thus it should be expected that the energy change of the *N*-oxide bond will result in stabilization of the formed intermolecular interactions.

Proton acceptor properties of *N*-oxide group

The starting point of discussion concerning the nature of the *N*-oxide bond was the ability of this bond to be applied for stabilization of crystal structures *via* hydrogen bonds in the crystal lattice. Hence, apart from the description of character of the nitrogen-oxygen bond another research aim was the analysis of proton acceptor properties of the *N*-oxide group.

The results of crystallographic studies of imidazole derivatives showed that the oxygen atom of this group is a good acceptor of intramolecular heteronuclear hydrogen bonds. However, a question arises whether or not the same phenomenon would be observed in the case of other types of intermolecular interactions and other aromatic *N*-oxides. In order to analyze this problem I examined the energy and structure of hydrogen bonds in selected model molecular complexes (B3LYP/aug-cc-pVTZ) [**H5**].

In all the examined systems the *N*-oxide group was found to be an effective proton acceptor forming hydrogen bonds of donor...acceptor distances and N-H...O angles that changed within the range of 2.65 – 2.76 Å and 174 – 178 °, respectively. The angle between the nitrogen-oxygen bond and the hydrogen atom is close to 120 °, which is related to the location of lone electron pairs of the oxygen atom. As a result of hydrogen bond formation the electron density transfer occurs from lone electron pairs of the *N*-oxide oxygen atom to the donor molecule due to which π donation is reduced. This leads to a weakening and lengthening of the nitrogen-oxygen bond and results in changes of stretching vibration frequencies of this bond in infrared direction (the red shift).

Positive values of the Laplacian of electron density $\nabla^2\rho_{BCP}(H...O)$ and negative densities of total energy $H_{BCP}(H...O)$ in critical point classify the analyzed interactions as hydrogen bonds of medium strength [38]. The bonds formed by imidazole *N*-oxide are a little stronger than those of pyridine *N*-oxide. Moreover, as concerns the examined pyridine *N*-oxides, when comparing *p*-amino and *p*-nitro derivatives, the influence of substituent effect in the acceptor molecule on the geometry and energy of the formed intermolecular interaction can be clearly seen.

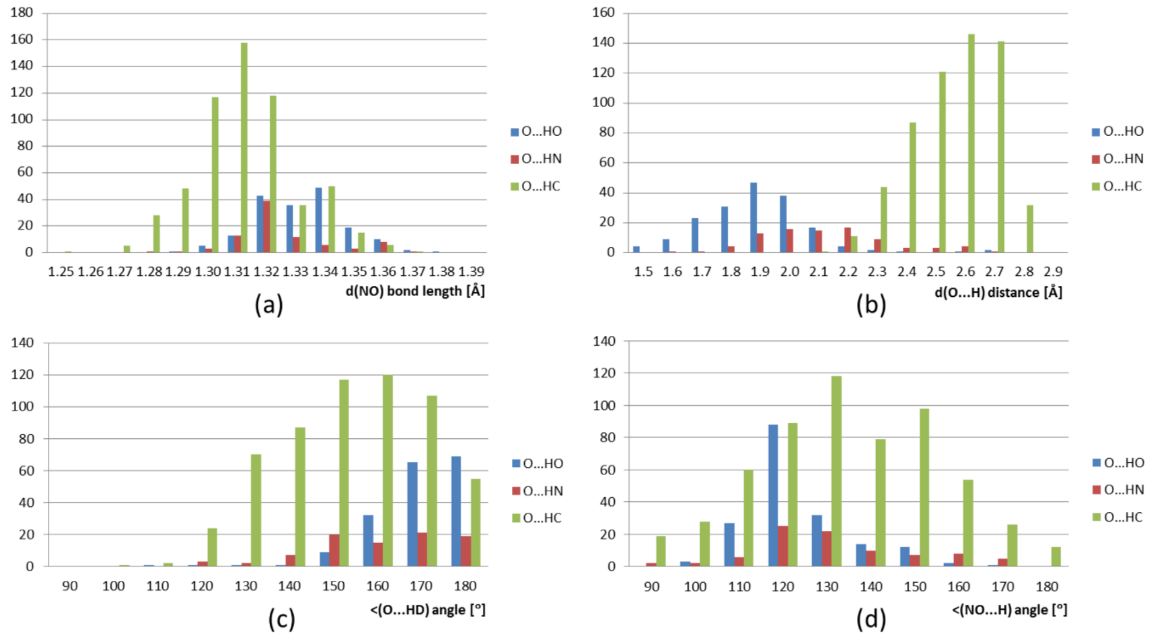


Figure 4. The range of changes of selected geometry parameters characterizing N-oxide hydrogen bonds D-H...ON based on the search of data from Cambridge Structural Database: the length of N-oxide bond d(NO) [Å] (a); the distance d(O...H) [Å] (b); the angle of hydrogen bond <(D-H...O) [°] (c); the angle <(H...NO) [°] (d).

In order to complement the performed investigations I carried out a review of structural data from Cambridge Structural Database (CSD) [39]. Crystallographic data indicate that functional groups containing the oxygen, nitrogen and carbon atoms can be donors of hydrogen bonds to the *N*-oxide group. In the crystalline state functional groups containing carbon atoms predominate, whereas those containing oxygen atoms are characterized by the shortest interatomic distances (Figure 4).

A comparison of geometry parameters of the observed interactions shows that the shortening of intermolecular distances is accompanied by a lengthening of the *N*-oxide bond and an increase of the angle of hydrogen bond. The values of angles with participation of hydrogen atom and the atoms of *N*-oxide group show the direction of interaction of proton donor groups with lone electron pairs of the oxygen atom. Similarly as in the examined model complexes they are close to 120 °.

Hydrogen bonds in structures of co-crystals

The conclusions drawn from the review of crystallographic database as well as those of the performed theoretical investigations encouraged me to make an attempt to obtain new structures stabilized by the *N*-oxide hydrogen bond. In view of the indicated substituent effects I concentrated on the use of simple *para* derivatives of the pyridine *N*-oxide and the reagents containing different proton acceptor groups in the synthesis of new multicomponent crystal structures (co-crystals).

The term "co-crystal" according to the approved definition [3] is a crystal structure which consists of at least two different components (atoms or molecules of chemical compounds) in a specific stoichiometric ratio which are solid state structures in environmental conditions. It should be emphasized that in practice the term "co-crystal" also includes hydrates, solvates, clathrates and salts.

With reference to crystal engineering, the interest in multicomponent structures results first of all from the fact that their components can be used as the molecular "building bricks" for designing multimolecular complexes or supramolecular structures [40-41]. Co-crystals are still little known and constitute about 0.5% of all known crystal structures [39].

The first project that I undertook in order to obtain and characterize molecular synthons in multicomponent structures was the synthesis of co-crystals of urea derivatives [**H2**]. Multiple structures of co-crystals and salts of this compound are known [42-47], but the characteristics of its substituted derivatives with regard to the formation of multicomponent structures were rather poorly examined in earlier publications [48-49].

The X-ray investigations that I carried out showed that in the crystal of the trichloroacetic acid - *N*-methylurea complex the reaction of proton transfer *via* hydrogen bonds leads to salt formation (Figure 5).

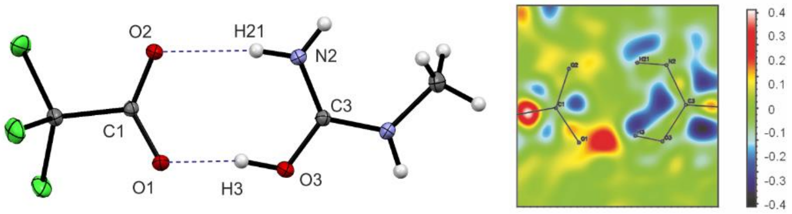


Figure 5. The crystal structure of the trichloroacetic acid - N-methyl urea complex showing a scheme of stabilizing hydrogen bonds O-H...O and N-H...O (on the left, dashed line); difference Fourier map in the area of those bonds (on the right), a range of colors presenting the changing electron density values [eÅ^{-3}]. The map was calculated for a model without hydrogen atoms participating in hydrogen bonds.

In the formed carboxylic acid - urea synthon a system of two intermolecular hydrogen bonds of type O-H...O and N-H...O stabilized with the +/-(CAHB) charge can be observed. Quantum chemical calculations

(MP2/6-311++G(d,p)) and topological analysis of electron density using the QTAIM theory allowed me to assess the strength of both bonds in the complex. Homonuclear interactions are classified as short hydrogen bonds (d(O...O) = 2.506(1) Å) of medium strength ($\nabla^2\rho_{BCP}(H...O) > 0$; $H_{BCP}(H...O) < 0$) [38], similarly as heteronuclear interactions which however are characterized by definitely longer distances (d(N...O) = 2.925(1) Å).

The NBO analysis shows that proton transfer via hydrogen bond O-H...O leading to an ionic structure exerts an effect on the energy increase of the other N-H...O bond in the complex. The examined hydrogen bonds are partly covalent in character, which is the result of orbital interactions between the electrons of lone electron pairs of the acceptor oxygen atoms and antibonding orbitals of the donor group. The changes in locations of those orbitals, due to the formation of a complex, are correlated with the determined charge transfer value (CT) between the donor molecule and the acceptor molecule. This value differs considerably for the neutral structure as compared with the ionic structure.

Among other intermolecular interactions which are responsible for the stabilization of crystal structure should be mentioned N-H...O hydrogen bonds and C-Cl...N halogen bonds.

In the next papers my interest in co-crystals included the afore-mentioned group of aromatic *N*-oxides. The multicomponent crystals containing simple derivatives of pyridine *N*-oxide were known earlier, to mention eleven structures of co-crystals of *p*-nitro and unsubstituted pyridine *N*-oxide and three salts: of hydrochloric acid, perchloric acid and trichloroacetic acid. The formation of systems that are stabilized by salt bridges, similarly as it was in the case of the described structure of *N*-methylurea co-crystal, is the result of proton transfer via hydrogen bond. Salt bridges were observed only for the unsubstituted pyridine derivative, which suggests that the strengthening of the *N*-oxide bond by resonance effects and the weakening of potential hydrogen bonds makes the reaction of proton transfer impossible.

As a result of the performed syntheses the other new multicomponent structures were obtained, including four structures with participation of *p*-nitropyridine *N*-oxide (Figure 6) [**H6**].

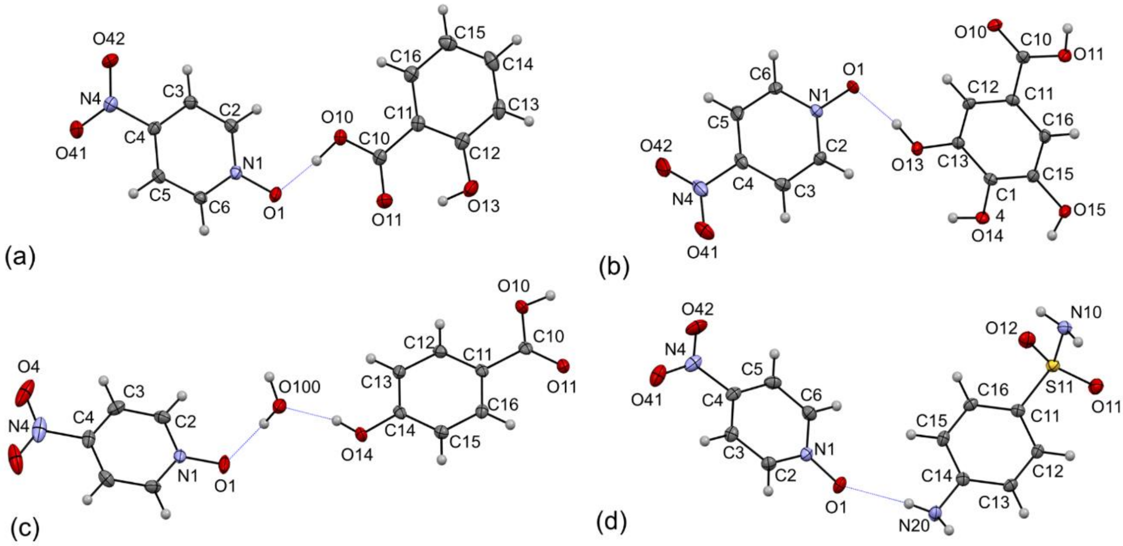


Figure 6. The crystal structure of complexes of p-nitropyridine N-oxide with selected proton donor reagents: salicylic acid (a); gallic acid (b); 4-hydroxybenzoic acid (c); and 4-aminobenzenesulphonamide (d); the dashed line shows hydrogen bonds to the N-oxide group.

Based on the analysis of crystallographic results it can be said that the *N*-oxide group forms various hydrogen bonds in which the carboxyl group, hydroxyl group, amine group and water molecules are the donors. These bonds are classified as the homo- and heteronuclear bonds. The homonuclear bonds are characterized by clearly shorter interatomic distances (d(O...O) = 2.44 ÷ 2.80 Å; d(N...O) = 2.82 ÷ 3.00 Å), which remains in agreement with the statistical analysis of data from CSD database presented earlier. A comparison of the geometry of hydrogen bridges in the obtained crystals with those available in database showed that in most of them double acceptor-type bifurcated bonds appear. Single bonds, particularly those in homonuclear bridges, are characterized by the distances between oxygen atoms shorter than 2.6 Å.

The crystallographic results were supplemented with the calculations based on quantum mechanics (B3LYP/6-311++G**) and the QTAIM method. In the examined systems the energy of homonuclear hydrogen bonds was found to be almost twice as high as that of heteronuclear ones and strongly dependent on the number of donor groups ($E_{HB}(OH...O_{single}) \cong 20$ kcal/mol; $E_{HB}(OH...O_{bifurcated}) \cong 10$ kcal/mol; $E_{HB}(NH...O_{bifurcated}) \cong 5$ kcal/mol).

A similar trend of the changes of stabilization energy of the examined molecular complexes was shown by the studies using the NBO method. Similarly as the QTAIM method, the NBO method estimates the charge flow connected with the formation of hydrogen bonds. Its value varies from 0.07 to 0.03 e, being considerably higher in the case of stronger homonuclear bonds.

Halogen bond as a characteristic interaction of the trichloromethyl group

Halogen bond is another interesting intermolecular interaction stabilizing the crystal structure. A tendency to form more or less stable complexes between halogen atoms and the atoms possessing lone electron pairs has been known for many years [55]. However, the term "halogen bond" did not appear until recently. The halogen bond is defined as an interaction between the halogen atom (X) which is covalently bonded to another atom (R) and the nucleophilic bond acceptor (Y) [56]. It is schematically presented as R-X...Y, where R-X denotes the donor group, by analogy to the hydrogen bond.

In the molecules of some compounds, on the surface of halogen atoms there appears an area of positive electrostatic potential on the σ orbital, known as the sigma hole [57]. Such an area is the result of reduced translocating of the nucleus along the R-X bond axis. When there is a sufficient deficiency of electrons, then the appearance of the sigma hole can result in energetically favorable interactions with the atoms possessing electron density excess (nucleophiles).

The above-presented interpretation of halogen bond formation was confirmed by experimental results which also showed that halogen bonds are strongly direction-specific. The location along the bond axis, i.e. according to the direction of the σ(R-X) orbital is attractive for nucleophiles and so the observed angle of halogen bond <(R-X...Y) is usually close to 180°. The appearance of interactions between X...Y atoms is accompanied by a shortening of distance between them to be lower than the sum of van der Waals radii [56].

In view of the electron charge flow from the acceptor to the donor the halogen bond, similarly as the hydrogen bond, can be classified as the Lewis acid-base interactions [58], however due to omnipresent hydrogen atoms in the structures of organic crystals the halogen bond is much less known. The energy of halogen bonds is usually small, being equal to several kcal/mol, i.e. on the level of weak hydrogen bonds. However, halogen bonds are observed to play an important role in various chemical systems and biological processes, and are also used in crystal engineering [59-60].

In hitherto-performed investigations of the afore-mentioned group of aromatic *N*-oxides the halogen donor properties of bromomethane (commonly known as methyl bromide) were assessed [**H5**]. The studies confirmed that the *N*-oxide group is able to form halogen bonds, but in the case of the analyzed model systems the interactions formed are accompanied by unconventional hydrogen bonds (Figure 7). The obtained values of stabilization energy of the complexes are small (less than 1 kcal/mol), which can be the result of rather weak Lewis acidity of the bromomethane molecule. Moreover, it is difficult to find unequivocally what is the relative contribution of each of the observed intermolecular interactions in that energy. The QTAIM characteristics of the analyzed halogen bonds show that they should be classified as weak interactions.

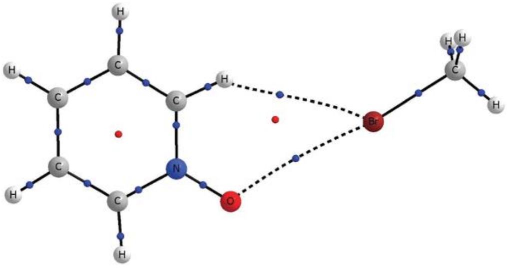
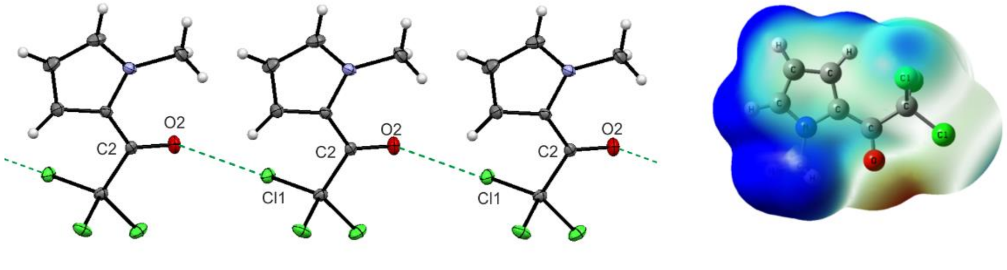


Figure 7. A molecular graph presenting the distribution of bond critical points (marked with navy-blue color) and the rings (marked with red color) in the pyridine N-oxide - bromomethane complex. Bond paths, including hydrogen interaction C-H...Br and halogen interaction C-Br...ON, are marked by a dashed line.

However, there are crystal structures in which close intermolecular contacts possessing halogen bond character with participation of oxygen atoms of the *N*-oxide groups of an aromatic derivative, for instance pyridine, were observed. Then the aromatic fragments of molecules are the donors of halogen bonds [39]. This suggests that systems of this type should be more useful for designing molecular complexes, and also shows the direction for further research.

In my investigations the crystal structure of 1-methyl-2-trichloroacetylpyrrole [**H1**] occurred to be particularly interesting. When comparing a scheme of intermolecular interactions in the crystals of that compound with analogical pyrrole derivatives my attention was drawn to short intermolecular contacts of type C-Cl...O (Figure 8). A more detailed analysis of geometry parameters showed that they are typical halogen bonds.



(a) (b)

Figure 8. A schematic diagram of intermolecular halogen bonds C-Cl...O in the crystal structure of 1-methyl-2-trichloroacetylpyrrole leading to the formation of a chain structure (a); MEP mapped in iso surface of electron density of 1-methyl-2-chloroacetylpyrrole - σ holes are visualized as blue areas around chlorine atoms (b).

The simultaneous presence of several chlorine atoms in the trichloromethyl group seems to favorably affect the ability of halogen bond formation *via* induction effects of the remaining chlorine atoms. The search of crystallographic database confirmed that the appearance of interactions of this kind is characteristic of compounds with the trichloromethyl substituent. No similar C-Cl...O halogen bonds were observed in mono- and dichloro- derivatives of the analyzed pyrrole derivative [61-62]. This allowed me to conclude that the presence of two remaining chlorine atoms in the molecule of the examined compound significantly affects (*via* induction effects) the deshielding of the interacting chlorine atom and strengthens its electrophilic properties as a halogen bond donor. It is confirmed by the analysis of the electrostatic potential distribution that reveals the existence of the σ hole on the C-Cl bonding axis (Figure 8).

It should be noted that in the described structure the cooperative effect of halogen bond was observed and described for the first time. This effect, which was known earlier for hydrogen bonds [63-66], is defined as the non-additive bond strengthening due to the participation of the donor or the acceptor in another similar intermolecular interaction. We can speak of the cooperative effect when interacting functional groups form chain structures or ring structures while the total energy effect is higher than the sum of energies of single interactions [65-67].

In the crystal structure of 1-methyl-2-trichloroacetylpyrrole the C-Cl...O interactions cause the formation of a repeated chain motive. As the donor group (trichloromethyl) and the acceptor group (carbonyl) are situated in close vicinity, the changes in electron density distribution in one of them can directly affect the other. Thus the participation of oxygen atom in the formation of halogen bond results in changes of density within the trichloromethyl group and in a strengthening of halogen interactions, which is revealed as a clear shortening of the chlorine-oxygen distance (2.941(1) Å) in comparison with the sum of van der Waals radii (3.27 Å). A review of CSD database showed that a similar situation can be observed in other crystal structures [**H1**].

The above-presented results of investigations drew my attention to the trichloromethyl substituent as a functional group which is able to form halogen bonds. I returned to the problem of halogen bonding in my publication describing structural studies of 2-trichloromethyl-3*H*-4-quinazoline [**H3**]. As the object of research I chose a compound which contains not only the trichloromethyl group in its molecule, but also other interesting functional groups that are capable of various intermolecular interactions.

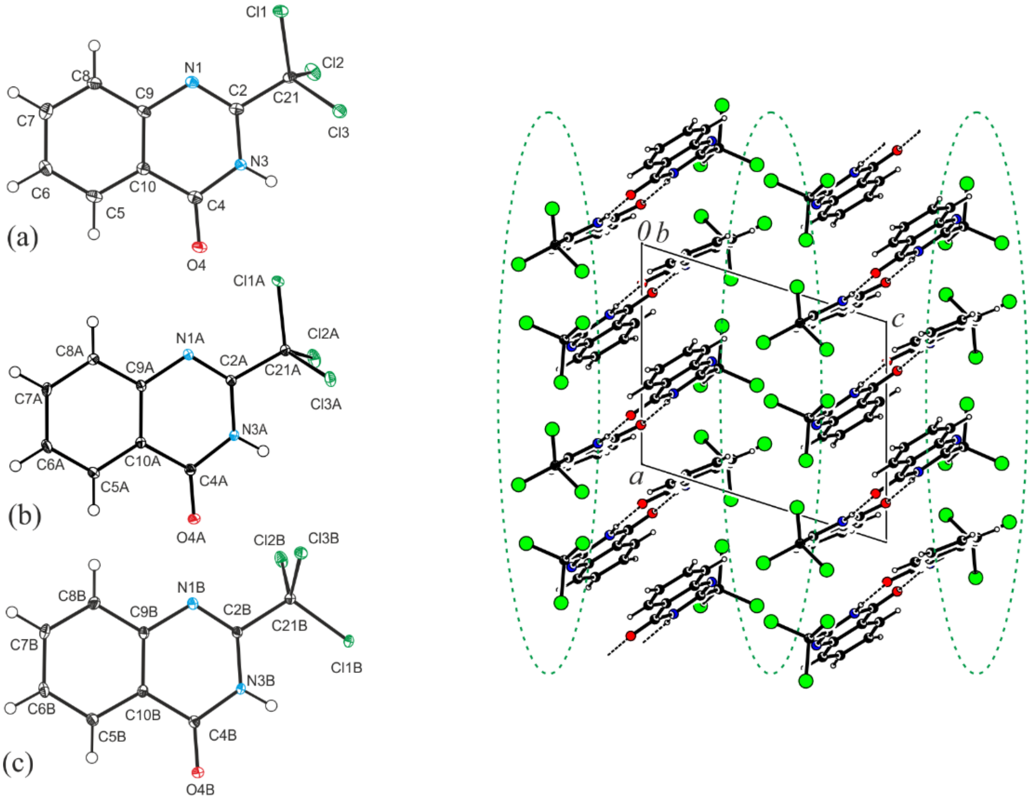


Figure 9. A comparison of conformations of the molecule of 2-trichloromethyl-3H-4-quinazoline (on the left): orthoorthorhombic form (a), monoclinic form, molecule A (b); monoclinic form, molecule B (c). On the right of the figure the layer structure of triclinic form is presented.

The quinazoline occurs in two polymorphic forms: orthorhombic form and triclinic form which are formed irrespectively of the applied solvent (methanol and toluene, respectively). In the triclinic structure in part of a symmetrically independent elemental cell there are two molecules: A and B. No significant differences were observed as concerns bond length and valence angle values between those molecules and the molecule that crystallizes in orthorhombic form. However, there are differences in molecular conformations which are due to different locations of chlorine atoms in the trichloromethyl group and a slightly different scheme of intermolecular interactions (Figure 9).

In both crystal structures the quinazoline molecules are joined to form similar dimers that are stabilized by a pair of hydrogen bonds of type N-H...O to the oxygen atom of the carbonyl group as an acceptor. They differ, however, by a different scheme of intermolecular interactions with participation of the chlorine atom. Many of those interactions are characterized by interatomic distances shorter than the sum of van der Waals radii. Yet, taking into account the above-mentioned angle criterion, only some of them can be classified as halogen bonds. They are: chlorine-nitrogen (C-Cl…N; d(Cl…N) = 3.098(2) Å) in orthorhombic form and chlorine-chlorine (C-Cl…Cl; d(Cl…Cl) = 3.494(1) Å), as well as chlorine - π electrons of the benzene ring in triclinic form.

Due to the existing intermolecular interactions in the crystals of both polymorphic forms a layer structure can be observed, namely the alternating two layers formed by the interacting chlorine atoms and by aromatic rings that are stabilized by hydrogen bonds and $\pi…\pi$ interactions.

In the trichloroacetic acid - *N*-methylurea co-crystal described earlier [**H2**] similar halogen bonds of type C-Cl...N appeared in the lattice of intermolecular interactions between the trichloromethyl group and the amine nitrogen atom (d(Cl…N) = 3.193(2) Å).

The performed investigations of halogen bonds of the trichloromethyl group were additionally supplemented by their description using Hirshfeld surface analysis.

Molecular Hirshfeld surfaces –quantitative analysis and visualization of the examined interactions

As a result of studies performed on the possibilities of using quantum chemical calculation methods in order to examine the distribution of electron density in the crystal the analysis of Hirshfeld surfaces (HS) was proposed [26].

The Hirshfeld molecule is determined by a set of points in space in which the summaric electron density derived from its atoms is equal to or exceeds the sum of contributions from all other molecules in the crystal. The Hirshfeld surface of a molecule in the crystal is defined by the boundary value known as the molecular weight function $w(r)$=0.5 [70]. In practice, for the known crystal structure the molecular weight function values, including the three-dimensional boundary of a molecule, are obtained using quantum chemical calculations [71].

In order to analyze the effects related to molecular packing and intermolecular interactions a normalized distance, d_{norm}, parameter is used which encodes information about close contacts of vicinal molecules [72]. The analysis of distribution of the values of this parameter allows one to verify intermolecular interactions.

The two-dimensional representation of the Hirshfeld surface, known as the fingerprint plot, reveals the number of points plotted against distance. Its analysis permits a selection of various types of intermolecular contacts, the determination of their per cent distribution and a comparison of the motives characterizing them.

The analysis of molecular Hirshfeld surfaces (HS) which is the source of information about various intermolecular interactions in crystals, has recently been widely applied for identifying and describing intermolecular contacts. I used it in my investigations to describe and compare intermolecular interactions of imidazole *N*-oxide derivatives [**H4**, **H8**], co-crystals of pyridine *N*-oxide derivatives [**H6**] and the compounds containing the trichloromethyl group [**H3**].

In the literature the authors point to characteristic motives of hydrogen bonds as the double, almost parallel, sharp and elongated peaks distributed symmetrically against the diagonal of the diagram [72]. Such a picture was observed for structures with typical hydrogen bonds which I examined, that is imidazole derivatives, quinazoline or the afore-mentioned co-crystals.

In the case of imidazole derivatives [**H4**, **H8**] only intermolecular contacts are revealed on Hirshfeld surfaces. These are first of all the interactions of type C-H…O and $\pi…\pi$. It can be observed that the obtained surfaces are similar as concerns their shape and distribution of the areas of close intermolecular interactions

(Figure 10). For example, for almost all derivatives positive d_{norm} values can be seen in the vicinity of C2 atom (marked with red color). However, it should be noted that this method is of little use as concerns the analysis of intramolecular hydrogen bonds of the *N*-oxide group.

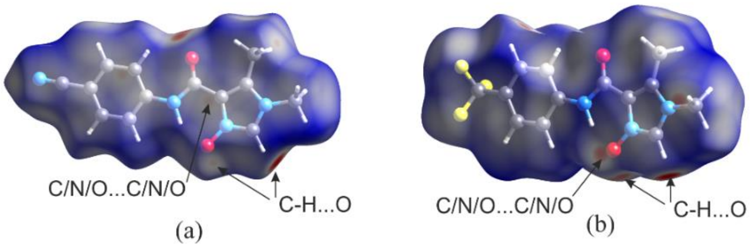


Figure 10. Molecular Hirshfeld surfaces: 3-oxide of N-(4-cyanomethylphenyl)-1,5-dimethyl-1H-imidazole-4-carboxamide (a); 3-oxide of N-(4-trifluoromethylphenyl)-1,5-dimethyl-1H-imidazole-4-carboxamide (b). The areas of short intermolecular contacts with d_{norm} values smaller than the sum of respective van der Waals radii are marked with red color.

The situation is entirely different in the case when intermolecular interactions were analyzed. For instance, in the molecule of *p*-nitropyridine *N*-oxides the presence of two different functional groups containing nitrogen-oxygen bonds (*N*-oxide and *N*-nitro) allowed me to compare their proton donor properties [**H6**]. The analysis of geometry parameters showed that the nitro group can also be the acceptor of hydrogen bonds, which was confirmed by the analysis of Hirshfeld surfaces, namely the areas of positive d_{norm} value were revealed near the nitro oxygen atoms (Figure 11).

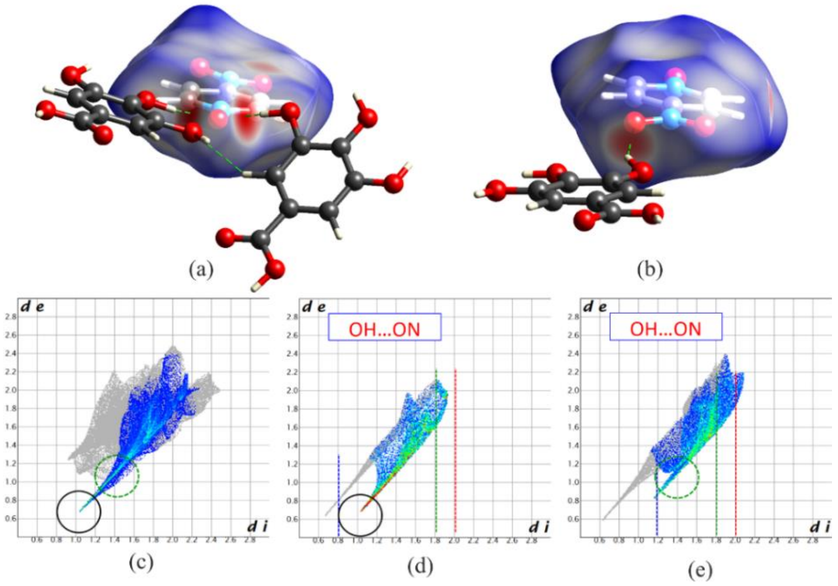
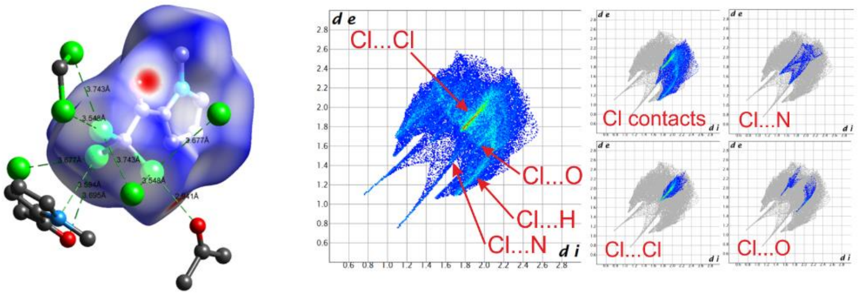


Figure 11. A comparison of the distribution of d_{norm} parameter values of molecular Hirshfeld surfaces near the N-oxide (a) and nitro (b) groups in the p-nitropyridine N-oxide - gallic acid co-crystal. The areas of d_{norm} values smaller than the sum of respective van der Waals radii are marked with red color. 2D histograms of intermolecular contacts in $O_{internal}$...H interactions performed on the basis of Hirshfeld surface analysis (c) with reference areas to N-oxide group (d) and nitro group (e).

When hydrogen bonds are present in the crystal they are usually accompanied by short intermolecular contacts of type H...O for both functional groups. The decomposition of the motives obtained on diagrams of Hirshfeld surfaces of *p*-nitropyridine *N*-oxides allows one to divide H...O contacts into those corresponding to the bonds to the *N*-oxide group or the nitro group as hydrogen bond acceptors. Apparently the motives of both functional groups are similar in shape. but they are located in different areas of the diagrams. The borders of the shortest and the longest intermolecular distances are marked with red color and blue color, respectively. It can be seen very clearly that the *N*-oxide group is able to form shorter and stronger interactions as compared with the nitro group. In the examined structures of co-crystals the contributions to H...O contacts result exactly from the presence of the nitro substituent, being equal to about 15% in the case of pyridine *N*-oxide and ranging from 20% to 30% for *p*-nitro substituted analogs.

I also used the methods based on Hirshfeld surface analysis to describe and depict halogen interactions [**H3**]. The analysis of intermolecular contacts in compounds containing the trichloromethyl group seemed to be particularly interesting, as in the literature there are no examples of interpretation of halogen bonds using this method and so there was no information that could serve as a point of reference during the investigations.

Halogen bonds of the trichloromethyl group that are present in the analyzed structures of pyrrole, quinazoline or the trichloroacetic acid - N-methylurea co-crystal are revealed on Hirshfeld surfaces in the form of areas with a positive d_{norm} value (marked with red color) whereas on two-dimensional representations they can be identified as the intensely colored area on the diagonal of the diagram (Figure 12).



(a) (b)

Figure 12. Schematic representation of short intermolecular contacts with participation of chlorine atoms (a) and the corresponding motives on 2D representations of Hirshfeld surfaces (b).

Quantitative analysis showed that in the examined crystals intermolecular contacts with participation of chlorine atoms have the greatest per cent contribution in the formation of a supramolecular structure (over 55%). In this group the % contribution of Cl...Cl contacts is of about 10%, those of Cl...O and Cl...N contacts strongly depend on the type of halogen bonds formed, whereas Cl...H contacts contribute in 30-41% and are over twice as numerous as H...H ones (5-15%).

The analysis of Hirshfeld surfaces also allows one to compare polymorphic variants [**H3**]. For the examined quinazoline derivative the differences were revealed first of all in contacts between hydrogen atoms. In the molecules these are always the terminal atoms, so the observed different shape of the corresponding areas on the diagrams is strictly connected with a different way in which the molecules are distributed in each of the examined crystal structures.

The location of hydrogen atom in hydrogen bonds

The presented results of studies were largely concerned with different aspects of intermolecular bonding interactions having the character of hydrogen bonds. These bonds can be characterized by energy, geometry or spectroscopic parameters. My investigations were always based on geometry and energy classifications. The former were based on crystallographic studies whereas the latter were obtained using the calculation methods of modern quantum chemistry. The analysis of energy was based on performing single point calculations (SP) which in turn were based on experimental geometry or the optimization of geometry of model systems. In order to assess the energy of hydrogen bonds a local energy measure was applied that resulted from electron density topological analysis at the critical point of H...A hydrogen bond. In order to appropriately find and characterize the critical point it is necessary to determine as exactly as possible the locations of atoms joined by a path of the bond on which it is situated (H and A).

Of all experimental methods, crystallographic studies are considered to be the most precise source of information about hydrogen bond geometry. Crystal X-ray diffraction allows one to establish the locations of atoms on the basis of the observed electron density maxima. The locations of the nucleus and maximum electron density usually overlap each other, but not in the case of hydrogen atom which formally has only one electron. In the covalent bond the average position of this electron as well as the observed electron density maxima are shifted towards the more electronegative atom. This results in a divergence between the nucleus location and that of the hydrogen atom established on the basis of maximum electron density. That is why in the X-ray method the determined values of hydrogen bond geometry parameters d(D-H) and d(H…A) are on assumption concerned with maximum electron density and not the location of hydrogen atom nucleus, and so in comparison with spectroscopic results they are burdened with error.

As can be seen by crystallographic studies based on X-ray crystal diffraction, the correct establishment of the location of hydrogen atoms is not a trivial task and any errors made on this stage can significantly affect the obtained hydrogen bond energies.

In order to solve the above problem neutron diffraction can be used. The results obtained by the neutronographic method of analysis are generally considered to be more reliable. The positions of hydrogen atoms in crystal structures determined by this method are characterized by higher precision and refer to the locations of atomic nuclei, similarly as for the other atoms [73-76]. However, due to technical requirements, high cost and much smaller availability of the neutronographic experiment it is not always possible to perform such measurements. That is why the number of crystal structures determined on the basis of neutronographic experiments is small (about 0.2% of all measurements) [39].

As it was already said in the introduction, the role of crystallographic investigations in the analysis of the structure of chemical compounds should not be underestimated. On the other hand, the calculation methods of modern quantum chemistry are becoming a common tool used in the analysis and interpretation of molecular structure. The combination of those two approaches affords new possibilities of describing the structure of various systems on a subatomic level. Hence, in multiple studies the geometries of molecules or intermolecular complexes known from crystallographic experiments are used as a starting point to advanced investigations based on quantum mechanical theories. In view of the above-described problem of the hydrogen atom location, in the case of X-ray results it is necessary to apply certain procedures that would "correct" the respective lengths of covalent bonds. In order to do this, covalent bonds are lengthened to attain the average standard neutronographic length [77-78], or the optimization of the systems in periodic conditions is performed [79]. The former method is much simpler and more common, and I used it in my hitherto-performed studies. However, it is generally known that in some cases the lengths of covalent bonds obtained by this procedure are not correct, in particular when strong hydrogen bonds are involved [80-82]. Moreover, in view of the increasing number of available results of neutronographic investigations, the values of calculated average lengths of covalent bonds have changed over the last few decades. For instance, for the hydroxyl group they changed from d(O-H) = 0.967 Å [77] to d(O-H) = 0.983 Å [78]. This is one of the reasons why the problem of establishing correct location of hydrogen atoms in the results obtained by X-ray diffraction has focused the attention of researchers for a long time.

In view of the above a question arises if there is a simple, fast and inexpensive way of appropriate correcting the bond length to hydrogen atoms. This question was always at the back of my mind during my crystallographic investigations. Finally, the quantum theory of atoms in molecules (QTAIM) occurred to be helpful.

Topological analysis of electron density allows one to determine the network of atomic attractors (electron density maxima) for the given distribution of atomic nuclei, and then to compare the distribution of both of them. I carried out such investigations both for the molecules whose geometry was known from an X-ray experiment and for selected model systems [**H7**]. It was found that in the case of non-hydrogen atoms there is no significant difference between the atom position and the attractor position.

The situation is completely different for hydrogen atoms. The calculations revealed considerable differences between the location of hydrogen atom nucleus and that of its electron density attractor (Δr), which ranged from 0.004 to 0.032 Å (Figure 13).

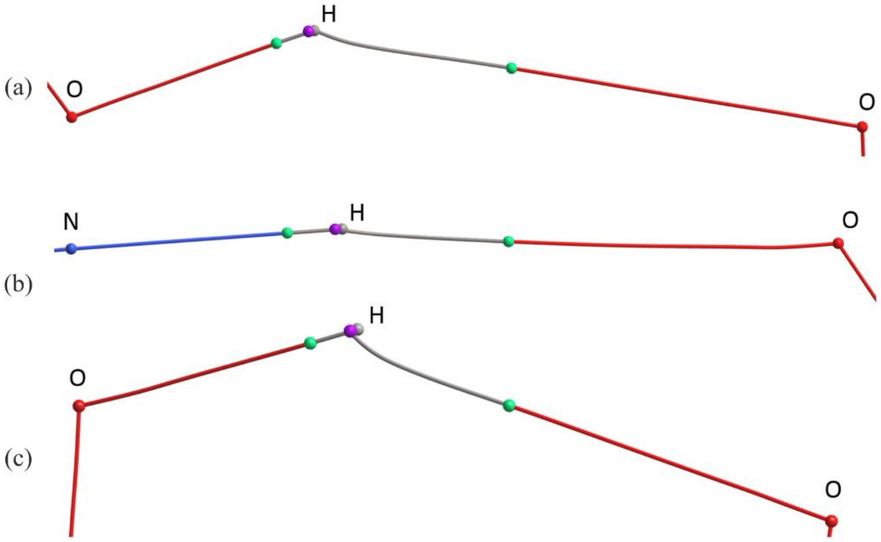


Figure 13. Fragments of molecular graphs in the areas of O-H…O and N-H…O hydrogen bonds showing the differences between the locations of hydrogen atom nuclei (marked with gray) and of the corresponding electron density attractors (marked with purple). The bond critical points are marked with green.

The observed differences were not dependent on the method of calculations (several popular functionals of electron density were tested: B3LYP, BHandHLYP, CAM-B3LYP, LC-ωPBE, M062X, M06L, ωB97XD in the functional base aug-cc-pVTZ), or even on whether or not the hydrogen atom participated in hydrogen bond. In the latter case the length of covalent bond changed significantly (the D-H donor bond was lengthened), but the observed Δr value did not change. On the other hand, the results differed significantly depending on the kind of element examined and formal atom hybridization with which the hydrogen atom is connected. The analysis of the obtained results allowed me to suggest a list of changes that would correct the length of covalent bonds to hydrogen bonds in order to appropriately adjust X-ray data to perform single point quantum chemical calculations.

Table 1. The observed differences Δr [Å] between the locations of hydrogen atom nuclei and those of the corresponding electron density attractors (maxima) (B3LYP/aug-cc-pVTZ calculation method).

formula	R-H covalent bond	Δr [Å]	formula	R-H covalent bond	Δr [Å]
LiH	Li-H	0.004	H_2CNH	N-H (sp^2)	0.020
BeH_2	Be-H	0.011	CNH	N-H (sp)	0.025
B_2H_6	B-H	0.012	H_2O	O-H	0.027
CH_4	C-H (sp^3)	0.016	HF	F-H	0.032
C_2H_4	C-H (sp^2)	0.016	PH_3	P-H	0.011
C_2H_2	C-H (sp)	0.018	H_2S	S-H	0.014
C_6H_6	C-H (aromatyczny)	0.016	HCl	Cl-H	0.017
NH_3	N-H (sp^3)	0.021	HBr	Br-H	0.014

In view of the performed investigations and the fact that in many computer programs the lengthening of respective covalent bonds has become an automatic computational procedure, it seemed to me particularly important to emphasize the problem of correct locations of hydrogen atoms in X-ray studies.

The importance of performed investigations and their potential application

The combination of experimental research technique, i.e. X-ray crystal diffraction, with the calculation methods used in modern quantum chemistry that I applied in my studies allowed me to perform a detailed characteristics of the title intermolecular interactions. Apart from the classical description of geometric properties of the crystal structure, my investigations also permitted me to perform the energy analysis of selected interactions and to assess the potential cooperative effects of those interactions. The combination of two different theories, that is QTAIM and NBO, allowed me to approach the analyzed problems from the point of view of two complementary methods.

My investigations were concentrated on several parallel trends which afforded new observations and conclusions. Therefore, in the presented series of publications several scientific achievements can be mentioned.

First of all, the recognition and description of the character of nitrogen-oxygen bond in the group of *N*-oxides can be treated as an important achievement. The performed studies allowed me to conclude that in aromatic *N*-oxides this bond has partly double character due to the interaction of lone electron pairs of the oxygen atom with antibonding orbitals. The characteristics of the nitrogen-oxygen bond and the role of this bond in stabilization of crystal structures are particularly important in view of growing interest in this type of compounds [83-88]. The above-described investigations are also directly related with the description of the properties of *N*-oxide group in intermolecular interactions which are responsible for the crystal architecture.

Structural observations made on the basis of analysis of model systems containing the molecules of *N*-oxides confirmed the results of the performed crystallographic investigations. The oxygen atom of the *N*-oxide group was found to be a good acceptor of different hydrogen bonds, and by appropriate choice of substituents in the *N*-oxide molecule it is possible to perform an essential modification of energy of hydrogen interactions, which can even result in a proton transfer reaction.

I also showed that the *N*-oxide group can be a halogen bond acceptor. However, the observed relatively low value of interaction energy as well as the results of the review of crystallographic database indicated that the role of halogen bond in stabilization of the *N*-oxide crystal structure is not as essential as that of hydrogen bond.

The situation is slightly different in the case of the trichloromethyl substituent. The trichloromethyl group can form relatively strong halogen bonds which because of the lack of hydrogen bonds are a significant agent affecting the crystal architecture and stabilizing the crystal structure. The performed crystallographic investigations confirmed that the cooperative effect involves halogen bonds in the same way as hydrogen bonds, which was pointed out earlier in the literature. The conclusions drawn in the publication encouraged other researchers to undertake studies on the cooperativity of halogen bonds [89-92].

The obtained results also allowed me to identify typical molecular synthons of selected functional groups and to characterize them as well as to carry out a detailed geometry and energy analysis. For instance, in the literature reports about the possibilities of formation of co-crystals with the derivatives of pyridine *N*-oxides were rather scarce. Moreover, there were no publications describing in a detailed way how the molecules formed aggregates in such structures and no descriptions of intermolecular structural motives that were being formed.

The molecular synthon which is formed as a result of interactions between the urea derivatives and the salts, especially one leading to the complexes stabilized by salt bridges, was little known earlier. However, it is well known that the identification of new synthons of intermolecular interaction while taking into account their energy aspect, can be applied in studies of molecular recognition and in crystal engineering.

The description of intermolecular interactions in molecular synthons that I examined was enriched by their characteristics which was established using Hirshfeld surface analysis. This seems to be particularly useful because the method has rapidly gained in popularity in the last years. The description and visualization of halogen bonds, or the graphic characteristics of proton acceptor properties of the *N*-oxide group provide new information that can be used for further interpretation of the obtained results and also for comparative purposes. In the presented publications I also showed that the method of Hirshfeld surfaces is helpful when we compare crystal structures of a series of derivatives, related compounds or polymorphic variations.

The proposition of correcting hydrogen atom locations known from the X-ray experiment is closely related to the problems concerning the characteristics of hydrogen bonding in the crystalline state. The appropriate establishment of hydrogen atom location in the hydrogen bridge is fundamental to the analysis of geometric properties of hydrogen bonds. In the case when quantum chemical calculations are engaged for clusters of the structure that is known from X-ray studies it is necessary to correct the length of covalent bonds to hydrogen atoms. So far the use of the average neutronographic lengths has been a standard approach. I have proposed the analysis of the problem based on QTAIM theory, which is a completely new approach. It allowed me to introduce a missing solution that is relatively simple and easy to use.

Summing up, the results presented in the series of publications, are new achievements in many aspects and seem to be important from the point of view of broadly understood structural chemistry. The purpose of my investigations was to contribute to gaining new knowledge as well as to expand the existing knowledge concerning the stabilization of intermolecular interactions in the crystalline state. Thanks to using advanced quantum theories the applied approach goes beyond the standard methodology of crystallographic studies. In conclusions of the presented review I showed the possibilities of application of the proposed solutions both in classical X-ray structural studies, methods of molecular recognition, and in investigations based on crystallographic results in which the calculation methods of modern quantum chemistry are engaged. In view of the fact that in recent studies a combination of the two approaches is frequently applied, this seems to be a direction of studies that is worth developing.

5. Other research achievements.

My scientific activity has been engaged in crystallography and the use of X-ray crystal structure analysis for many years. For some time now I have added to my research methods the calculation methods based on modern quantum chemistry. The purpose of the performed studies was first of all to know and describe the molecular structure and crystal architecture of various organic, metal-organic, and complex compounds.

The investigations performed together with my co-workers at the present Department of Theoretical and Structural Chemistry of University of Lodz afforded multiple co-authored publications. Among them particularly interesting are the works concerning the analysis of experimental electron density distribution in crystals based on high-resolution diffraction measurements that were performed at the Deutsches Elektronen-Synchrotron (DESY) research center in Hamburg, Germany ([P28] and [P29] Annex No. 3).

As my special scientific achievements I would also like to mention the investigations performed in cooperation with the research workers of Department of Organic Chemistry, Faculty of Chemistry, University of Lodz. These studies afforded numerous publications in metal-organic chemistry ([P3], [P6], [P8], [P14], [P15], [P17], [P18], [P19], [P20], [P22], [P23], [P25], [P30], [P31], [P33], [P34] and [P35] Annex No. 3). Among them interdisciplinary projects predominate in which I determined the molecular and crystal structure of new metallocenes. The complex compounds of iron, tungsten, molybdenum and ruthenium that are potential pharmacological markers were examined.

I also carried out important structural investigations of copper and platinum complexes and their heterocyclic ligands. The studies were performed in cooperation with research workers from Department of Bioinorganic Chemistry, Medical University of Lodz ([P2], [P4], [P5], [P9], [P10], [P12], [P16], [P21], [P26], [P27] and [P32] Annex No. 3). They are the alkylating cytostatic compounds also acting as potential anti-cancer drugs.

My scientific achievements include 44 publications in peer reviewed journals, of which 25 were published after obtaining my Ph.D. degree (a complete list can be found in Annex No. 3). Joint scientific achievements afforded multiple teamwork awards, among them the rewards granted by the Rector of University of Lodz, Rector of Medical University of Lodz and Minister of Health of Poland.

A. Rybarczyk - Pirek

References

1. G.R. Desiraju, "*Crystal Engineering: The Design of Organic Solids*", Elsevier, Amsterdam 2008.
2. G.R. Desiraju, T. Steiner, "*The weak hydrogen bond in structural chemistry and biology*", Oxford University Press, New York 1999.
3. Z. Bojarski, M. Główka, Z. Jaskólski, K. Ławniczak-Jabłońska, K. Łukaszewicz, B. Oleksym, „*Słownik Terminów Krystalograficznych*", Wydawnictwo Politechnika Łódzka, Łódź 2003.
4. G. P. Stahly, *Cryst. Growth & Des.* (2009) 9, 4212.
5. G.P. Stahly, *Cryst. Growth & Des.* (2007) 7, 1007.
6. M.J. Zaworotko, *Crystal Growth & Design* (2007) 7, 616.
7. C.B. Aakeroy, M.E. Fasulo, J. Desper, *J. Mol. Pharmaceutics* (2007) 4, 317.
8. M.J. Zaworotko, *Cryst. Growth & Des.* (2007) 7, 4.
9. R.F.W. Bader, "*Atoms in molecules - a quantum theory*", Oxford University Press, Oxford 1994.
10. F. Weinhold, F. Landis (2005) "*Valency and bonding. A natural bond orbital donor–acceptor perspective*" Cambridge University Press, Cambridge 2005.
11. M.A. Spackman, D. Jayatilaka, *CrystEngComm* (2009) 11, 19.
12. G.A. Jeffrey, W. Saenger, "*Hydrogen Bonding in Biological Structures*", Springer-Verlag, Berlin, 1991
13. G.A. Jeffrey, "*An Introduction to Hydrogen Bonding*", Oxford University Press, New York, 1997.
14. G.R. Desiraju, *Acc. Chem. Res.* (2002) 35, 565.
15. E. Arunan, G,R. Desiraju, R.A. Klein, J. Sadlej, S. Scheiner, I. Alkorta, D.C. Clary, R.H. Crabtree, J.J. Dannenberg, P. Hobza, H.G. Kjaergaard, A.C. Legon, B. Mennucci, D.J. Nesbitt, *Pure Appl. Chem*. (2011) 83, 1619.
16. T. Steiner, *Angew. Chem. Int. Ed*. (2002) 41, 48.
17. P. Gilli, V. Bertolasi, V. Ferretti, G. Gilli, *J. Am. Chem. Soc.* (1994) 116, 910.
18. G. Gilli, V. Bertolasi, V. Ferretti, P. Gilli, *Acta Crystallogr*. (1993), B49, 564.
19. G. Gilli, P. Gilli, *J. Mol. Struct*. (2000) 552, 1.
20. S.J. Grabowski, W.A. Sokalski, J. Leszczyński, *J. Phys Chem. A* (2006) 14, 4772.
21. S.J. Grabowski, *Chem. Rev*. (2011) 111, 2597.
22. C.A. Morrison, M.M. Siddick, P.J. Camp, C.C. Wilson, *J. Am. Chem. Soc.* (2005) 127, 4042.
23. M. Garcia-Viloca, A. Gonzalez-Lafont, J.M. Lluch, *J. Am. Chem. Soc.* (1997) 119, 1081.
24. A. Filarowski, A. Koll, T. Głowiak, *J. Chem. Soc. Perkin Trans*., 2. (2002) 835.
25. M. Jasiński, G. Mlostoń, A. Linden, H. Heimgartner, *Helv. Chim. Acta* (2008), 1916.
26. M.C. Etter, *Acc. Chem. Res*. (1990) 23, 120.
27. V. Bertolasi, V. Ferretti, P. Gilli, G. Gilli, Y.M. Issa, O.E. Sherif, *J Chem. Soc. Perkin Trans. 2,* (1993) 2223.
28. P. Gilli, V. Bertolasi, V. Feretti, G. Gilli, *J. Am. Chem. Soc.* (2000) 122, 10405.
29. E. Espinosa, E. Molins, C. Lecomte, *Chem. Phys. Lett.* (1998) 285, 170.
30. P. Gilli, V. Bertolasi, V. Feretti, G. Gilli, *J. Am. Chem. Soc.* (2002) 124, 13554.
31. P.L.A. Popelier „Atoms in Molecules, an Introduction" Prentice Hall, 2000.
32. R.J. Gillespie, I. Bytheway, E.A. Robinson, *Inorg. Chem.* (1998) 37, 6884.
33. A.E. Reed, P. v R. Schleyer, *J. Am. Chem. Soc.* (1990) 112, 1434.
34. I. Love, *J. Phys. Chem. A* (2006) 110, 10507.
35. D.B. Chesnut, *Chem. Phys.* (2003) 291, 141.
36. J.A. Dobado, H. Martinez-Garcia, J. Molina, M.R. Sundberg, *J. Am. Chem. Soc.* (1998) 120, 8461.
37. S. Youssif, *Archivoc* (2001) 242.
38. I. Rozas, I. Alkorta, J. Elguero, *J. Am. Chem. Soc*. (2000) 122, 11154.

39. F. H. Allen, Acta Crystallogr. (2002) B58, 380.
40. S.L Childs, G.P. Stahly, A. Park, *Mol. Pharm*. (2007) 4, 323.
41. M. Du, Z-H. Zhang, X-J. Zhao, H. Cai, *Cryst. Growth Des*. (2006) 6, 114.
42. V. Videnova-Adrabinska, M.C. Etter, *J. Chem. Crystallogr*. (1995) 25, 823.
43. G. Smith, K.E. Baldry, K.A. Byriel, C.H.L. Kennard, *Aust. J. Chem.* (1997) 50, 727.
44. Y.V. Nelyubina, K.A. Lyssenko, D.G. Golovanov, M.Y. Antipin, *CrystEngComm.* (2007) 9, 991.
45. A.J. Cruz-Cabeza, G.M. Day, W. Jones, *Chem. Eur. J.* (2008) 14:8830.
46. A. Alhalaweh, S. George, D. Bostrom, S.P. Velaga, *Cryst. Growth Des*. (2010) 10, 4847.
47. M. Gryl, A. Krawczuk-Pantula, K. Stadnicka, *Acta Crystallogr.* (2011) B67, 144.
48. J.H. Bryden, *Acta Crystallogr.* (1957) 10, 714.
49. S. Harkema, J.H.M. Ter Brake, H.J.G. Meutstege, *Acta Crystallogr*. (1979) B35, 2087.
50. P. Ballesteros, R. M. Claramunt, T. Cafiada, C. Foces-Foces, F. Hernandez Cano, J. Elguero, A. Fruchier, *J. Chem. Soc. Perkin Trans. 2* (1990) 1215.
51. J. Hartung, R. Kneuer, M. Schwarz, I. Svoboda, H. Fueß, *Eur. J. Org. Chem.* (1999) 97, 2106
52. A. Szemik-Hojniak, T. Glowiak, A. Puszko, Z. Talik, *J. Mol. Struct*. (1998) 77.
53. J.E. Leffler*, Science* (1953) 117, 340.
54. G.S. Hammond, *J. Am. Chem. Soc*. (1955) 77, 334.
55. F. Guthrie, *J. Chem. Soc*. (1863) 16, 239
56. G.R. Desiraju, P.S. Ho, L. Kloo, A.C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati, K. Rissanen, *Pure Appl. Chem.* (2013) 85, 8, 1712.
57. P. Politzer, J.S. Murray, T. Clark, *Phys. Chem. Chem. Phys*. (2010) 12, 7748.
58. P. Metrangolo, H. Neukirch, T. Pilati, G. Resnati, *Acc. Chem. Res*. (2005) 38, 386.
59. E. Corradi, S.V. Meille, T.M. Messina, P. Metrangolo, G. Resnati, *Angew. Chem. Int. Ed*. (2000) 39, 1782.
60. P. Metrangolo, T. Pilati, G. Resnati, *CrystEngComm.* (2006) 8, 946.
61. A.T. Dubis, M. Domagała, S.J. Grabowski, *New J. Chem*. (2010) 34, 556.
62. S.J. Grabowski, T.A. Dubis, D. Martynowski, M. Główka, M. Palusiak, J. Leszczyński, *J. Phys. Chem A* (2004) 108, 5815.
63. A. Karpfen, *Adv. Chem. Phys*. (2002) 123, 469.
64. R. D. Parra, S.Bulusu, X.C. Zeng, *J. Chem. Phys*. (2003) 118, 3499.
65. S. Xantheas, *J. Chem. Phys.* 100 (1994) 7523.
66. S. Xantheas, *Chem. Phys*. (2000) 258, 225.
67. L. Albrecht, R.J. Boyd, Compt. And Theoretical Chem. (2015) 1053, 328.
68. L. Albrecht, S. Chowdhury, R.J. Boyd, J. Phys Chem. A (2013) 117, 10790.
69. J.M. Guevara-Vela, R. Chavez-Cavillo, M. Garcia-Revilla, J. Hernandez-Trujillo, O. Christansen, E. Francisco, A.M. Pendas, T. Rocha-Rinza, *Chem. Eur. J.* (2013), 19, 14304.
70. J.J. McKinnon, M.A. Spackman, A.S. Mitchell, *Acta. Crystallogr*. (2004) B60, 627.
71. F.L. Hirshfeld, *Theor. Chem. Acta* (1977) 44, 129.
72. J.J. McKinnon, D. Jayatilaka, M.A. Spackman, *Chem. Commun*. (2007) 3814.
73. T. Steiner, W. Saenger, *J. Am. Chem. Soc.* (1992) 114, 10146.
74. Hibbs, D. E.; Overgaard, J.; Piltz, R. O. Org. Biomol. Chem. 2003,1, 1191.
75. A.O. Madsen, S. Mason, S. Larsen, *Acta Crystallogr*. (2003) B59, 653.
76. A.O. Madsen, C. Flensburg, R.F. Stewart, S. Larsen, H.O. Sørensen, *Acta Crystallogr*., (2004) A60, 550.
77. F.H Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, *J. Chem. Soc. Perkin Trans II* (1987), S1
78. F.H. Allen, J.I. Bruno, *Acta Crystallogr*. (2010) B66, 380.
79. R. Dovesi, R. Orlando, A. Erba, C.M. Zicovich-Wilson, B. Civalleri, S. Casassa, L. Maschio, M. Ferrabone, M. De La Pierre, P. D'Arco, Y. Noel, M. Causa, M. Rerat, B. Kirtman, *Int. J. Quantum Chem*. (2014) 114, 1287.
80. I.S. Konovalova, Y.V. Nelyubina, K.A. Lyssenko, B.V. Paponov, O.V. Shishkin, *J. Phys. Chem. A* (2011) 115, 8550.
81. B.B. Averkiev, A.A. Korlyukov, M.Y. Antipin, A.B. Sheremetev, T.V. Timofeeva, *Cryst. Growth Des*. (2014) 14, 5418.
82. V.Z. Zhurov, A.A. Pinkerton, *J. Phys. Chem. A* (2015) 119, 13092.
83. G. Powis, M.M. Ames, J.S. Kovac *Cancer Res.* (1979) 39; 3564.
84. C. Herbert, A. Hettiaratchi, D.C. Webb, P.S. Thomas, P.S. Foster, R.K. Kumar *Clinical Experiment. Allergy* (2008) 38, 847.
85. J.R. Amsden, P.O. Gubbins, S. McConnell, E. Anaissie, *Antimicrob. Agents Chemother*. (2013) 57, 3420.
86. W.A. Denny, *Curr. Med. Chem.* (2004) 4, 395.
87. E. Torres et al, *Eur. J. Med. Chem*. (2013) 66, 324.
88. M.E Sawaya, J. Shapiro *Clinics in Derm*. (2000) 18, 177.
89. X.C. Yan, P. Schyman, W.L. Jorgensen, *J. Phys. Chem. A* (2014), 118, 2820.
90. M. Domagała, P. Matczak, M. Palusiak, *Comp. Theoret. Chem*. (2012) 998, 26.
91. J. George, V.L. Deringer, R. Dronskowski, *J. Phys. Chem. A* (2014), 118, 3139.
92. J. Dominikowska, F.M. Bickelhaupt, M. Palusiak, C. Fonseca Guerra, *Chem. Phys. Chem*. (2016) 17, 474.