

## **Self-presentation**

Dr Łukasz Dobrzycki

*Structural investigations on disordered crystals  
with special emphasis on hydrates of aliphatic amines*



University of Warsaw, Faculty of Chemistry  
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## 1. Given name and surname

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- |      |              |   |
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| 2009 | – PhD degree | „On Crystal Structures of Inorganic-Organic Hybrid Salts with Layered and Rod Architecture Type”<br>Supervisor: prof. dr hab. Krzysztof Woźniak |
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## 4. Scientific achievement submitted for habilitation procedure:

### a) Title:

*„Structural investigations on disordered crystals with special emphasis on hydrates of aliphatic amines”*

### b) List of scientific papers the achievement is based:

- H1.** Dobrzycki, Ł.; Socha, P.; Ciesielski, A.; Boese, R.; Cyrański, M. K., „Formation of Crystalline Hydrates by Nonionic Chaotropes and Kosmotropes: Case of Piperidine”, *Crystal Growth & Design*, **2019**, *19*, 1005-1020  
**DOI: 10.1021/acs.cgd.8b01548** IF<sup>2017</sup>: 3.972, MNiSW<sup>2016</sup>: 35
- H2.** Dobrzycki, L., „Towards clathrates. 2. The frozen states of hydration of *tert*-butanol”, *Zeitschrift für Kristallographie - Crystalline Materials*, **2018**, *233*, 41-49  
**DOI: 10.1515/zkri-2017-2074** IF<sup>2017</sup>: 1.263, MNiSW<sup>2016</sup>: 25
- H3.** Socha, P; Dobrzycki, L., „Crystal structure of 4,4'-bipiperidinium dichloride 0.12 hydrate, C<sub>10</sub>H<sub>22</sub>N<sub>2</sub>Cl<sub>2</sub>·0.12 H<sub>2</sub>O”, *Zeitschrift für Kristallographie - NCS*, **2016**, *231*, 693-694  
**DOI: 10.1515/ncrs-2015-0234** IF<sup>2016</sup>: 0.152, MNiSW<sup>2016</sup>: 15
- H4.** Dobrzycki, Ł.; Pruszkowska, K.; Boese, R.; Cyrański, M. K., „Hydrates of Cyclobutylamine: Modifications of Gas Clathrate, Types sl and sH”, *Crystal Growth & Design*, **2016**, *16*, 2717-2725  
**DOI: 10.1021/acs.cgd.5b01846** IF<sup>2016</sup>: 4.055, MNiSW<sup>2016</sup>: 35
- H5.** Dobrzycki, L.; Taraszewska, P.; Boese, R.; Cyranski, M. K., „Pyrrolidine and Its Hydrates in the Solid State”, *Crystal Growth & Design*, **2015**, *15*, 4804-4812

**DOI: 10.1021/acs.cgd.5b00527**

IF<sup>2015</sup>: 4.425, MNI<sup>2016</sup>: 35

- H6.** Dobrzycki, Ł.; Taraszewska, P.; Boese, R.; Cyranski, M. K.; Cirkel, S. A., „Towards Clathrates: Frozen States of Hydration of *tert*-Butylamine”, *Angewandte Chemie-International Edition*, **2015**, *54*, 10138-10144

**DOI: 10.1002/anie.201412331**

IF<sup>2015</sup>: 11.709, MNI<sup>2016</sup>: 45

- H7.** Cyrański, M. K.; Jamróz, M. H.; Rygula, A.; Dobrowolski, J. Cz.; Dobrzycki, Ł.; Baranska, M., „On two alizarin polymorphs”, *CrystEngComm*, **2012**, *14*, 3667-3676

**DOI: 10.1039/c2ce06063a**

IF<sup>2012</sup>: 3.879, MNI<sup>2016</sup>: 35

- H8.** Hoser, A. A.; Dobrzycki, Ł.; Gutmann, M. J.; Woźniak, K., „Charge Densities of Two Polymorphs of Hydrated 1,8-Bis(dimethylamino)naphthalene Hydrochloride-Similarities and Differences”, *Crystal Growth & Design*, **2010**, *10*, 5092-5104

**DOI: 10.1021/cg1007445**

IF<sup>2010</sup>: 4.390, MNI<sup>2016</sup>: 35

## c) Presentation of the aim of the work and obtained results.

### Introduction

The series of publications presented as the habilitation thesis work refers in the greater part to the structural studies of hydrates of small organic compounds that are liquid at room temperature (aliphatic amines, tetrahydrofuran) or easily melting solids, like *tert*-butanol. However, the term hydrate has a very broad meaning. In the general case, hydrates can be considered as systems containing water in their structures. The hydrate defined in this way does not necessarily have to be a solid with a crystalline or amorphous structure. The presence of water can be realised in a variety of ways.

#### Hydrates I – water covalently "embedded" in the structure of a molecule

Hydrates of some organic compounds can be understood as reaction products of anhydrides with water. For example, acetic acid is a hydrate of acetic anhydride. Another example of such a hydrate may be chloral hydrate - a crystalline solid used once as a sedative. In the case of hydrates of this type, we are obviously aware that water is not present in the structure as a molecule but in the form of OH\* and H\* fragments. Other hydrates of this type may be alcohols, *e.g.* methanol or ethanol, which can be viewed as the reaction products of water and the corresponding alkene. From a historical point of view, carbohydrates containing carbon and water in a 2:1 molar ratio can also be considered as hydrates. Indeed, treating, for example, glucose with strong sulfuric acid leads to its irreversible dehydration, resulting in carbon. As in the case of chloral hydrate, the water molecule in hydrocarbons, does not exist in a free form. Thus, these hydrates are simply molecules in which it is possible to distinguish water in the molecular formula; although water molecules are not explicitly found in the structure (*e.g.* glucose = C<sub>6</sub>H<sub>12</sub>O<sub>6</sub> = C<sub>6</sub>(H<sub>2</sub>O)<sub>6</sub> ).

#### Hydrates II – water acting as a complexing agent.

Another group of hydrates, where water is present but with well-preserved structure of the molecule, are hydrates with H<sub>2</sub>O molecules acting as ligands surrounding the central ion of the metal cation. In these hydrate structures, water forms coordinative bonds with the cation using the lone electron pairs on the oxygen atom of the H<sub>2</sub>O molecule. Examples of such systems include the hydrates of inorganic salts, *e.g.* transition metal halides. Well-known compounds of this kind are cobalt (II) chloride hydrates containing a different amount of water molecules in their structures. The salt may exist in anhydrous form and as a series of hydrates: dihydrate [1], tetrahydrate [2] or hexahydrate [2]. In aqueous solutions of cobalt (II) salts, we can expect fully-hydrated metal ions. It is rather obvious that, due to the different coordination of the central ion, the hydrates may differ in their properties; one example being their colours. Anhydrous cobalt (II) chloride is used as a moisture detector, the presence of water and the formation of hydrate changes its colour from blue to pink. An interesting example are the cerium (III) sulphate (VI) compounds which form a whole range of differently hydrated salts. Cerium (III) sulphate (VI) forms, for example, salts containing 2, 4, 5, 7, 8, 9 or 12 water molecules. Perhaps it is not a record

number of hydrates; however, all lanthanide (III) sulphate (VI) compounds share a very interesting feature - their solubility in water decreases with an increasing temperature [3] - which is undoubtedly linked to their negative enthalpies of solvation. Hydrates of this type containing coordinated water molecules are extremely important in the construction industry, since both cement and semihydrate or anhydrous calcium sulphate(VI), when subjected to the hydration process, form a solid strong mass after the binding process is completed. The strength, especially for compression, is extremely high in the case of concrete where appropriate calcium silicates (alite, belite, etc.) are subjected to hydration [4]. It is worth mentioning that hydrates of this type may undergo reversible dehydration. Hydrates in which the water molecules are coordinated to metal cations forming complex ions are analogous to complexes containing  $\text{NH}_3$  molecules or organic derivatives of water molecules:  $\text{R-OH}$  (alcohols);  $\text{R-NH}_2$  (amines);  $(\text{R-CO}_2^-)_n\text{M}^{n+}$ ; (carboxylates); or more complex species. In these kinds of systems, as well as in hydrates of cobalt (II) chloride, the O...Co contact distances are comparable and range within the limits of 2.0 Å - 2.2 Å, being typical for these cases.

### Hydrates IIa - hydronium ion

Extremely interesting cases are hydrates where the water molecule can coordinate the proton, which can not exist in a free form in aqueous solutions or in the crystal lattice. Such a proton hydrate ( $\text{H}_3\text{O}^+$ ) is called the hydronium ion. This ion may be additionally hydrated leading to various structures such as *Eigen* or *Zundel* formation [5]. The *Zundel* ion or its more hydrated analogues can be found in solids [6]. The typical distance between the oxygen atoms in the  $\text{H}_5\text{O}_2^+$  ion ranges from 2.4 - 2.5 Å.

### Hydrates III - water embedded by hydrogen bonds

Increasing the amount of water in hydrate salt structures leads to the saturation of the coordination ion sphere of the central ion and the appearance of more weakly-bonded water molecules forming hydrogen bonds [7]. Indeed, in the structure of the  $\text{CoCl}_2$  hexahydrate, some of the water molecules that are not involved in the coordination of the cations form hydrogen bonds with  $[\text{CoCl}_2(\text{H}_2\text{O})_4]$  units, leading to stabilization of the structure. Such structures containing water molecules, whose presence is stabilized by the formation of hydrogen bonds with the hydrated molecule but possibly also with other  $\text{H}_2\text{O}$  molecules, can be considered as another group of water-containing systems. While the hydrates containing water covalently embedded or coordinatively bonded may exist in solid, liquid or gas form with little effect of the aggregation on the structure of such a hydrate, the systems where the water molecules form hydrogen bonds are less stable and hence can be more easily dehydrated. It is also important to note that, in the liquid phase, dynamical water-hydrated molecular interactions are present. This type of crystalline hydrate is extremely common, especially when organic compounds are taken into account. Undoubtedly, this is related to a huge diversity of this type of system. Their number increases almost daily in the Cambridge Structural Database (database of organic compounds structures) CSD [8], where around 12% of all deposited systems are hydrates of this type.

These systems are particularly important for the pharmaceutical industry. The active pharmaceutical ingredient (API) in a crystalline solid is often present in co-crystalline form [9] or as hydrates with water, which are incorporated to the structure by weak interactions (hydrogen bonds, van der Waals *etc.*). Their formation suggests the possibility of patenting specific crystalline polymorphic forms, each being different from the original product. In addition, the presence of water molecules in the structure affects the physical properties of the crystal: habit, durability, solubility, *etc.*, which obviously has an impact on the formulation of a given drug [10]. Hydrates belonging to this group do not necessarily have to be composed of uncharged particles. Obviously, the crystals can be formed from ions stabilized by additional hydrogen bonds with water molecules.

Water molecules, even if only weakly bonded, play a crucial role in the structures of peptides and proteins. The structures of macromolecules, whether in aqueous solutions, cytoplasm or crystals, are stabilized by H<sub>2</sub>O molecules constituting a hydration shell. In protein crystals, water molecules are often extremely disordered and the whole structure is more like a liquid. An example of a relatively stable but at the same time tasty hydrate may be jelly, *e.g.* a fruit jelly formed during the gelation of water-soluble gelatin, which is a mixture of proteins and peptides. Protein crystals, due to their large macromolecular size, high water content and structural disorder, are very specific. In the case of typical organic compounds (of small or moderate size) with large contents of H<sub>2</sub>O molecules in addition to hydrogen bonds formed between the hydrated molecule and water, well-defined hydrogen bonds between H<sub>2</sub>O molecules can also be present. An example of such a system is pyridine trihydrate [11] where, between the layers formed by water molecules, layers of organic compound are present. An increase of the number of water molecules, *i.e.* the dilution of the hydrated molecule, leads to a three-dimensional network of hydrogen-bonded H<sub>2</sub>O molecules. This is observed, for example, in the heptahydrate of *tert*-butanol [12] and is particularly evident in the 6½ hydrate of propylamine [13], where the organic compounds are bound to a network of water molecules through hydrophilic functional groups, while their hydrophobic fragments are found in the niches formed by H<sub>2</sub>O molecules. The motifs of various possible networks of water molecules in hydrates of organic compounds are described in reference 14. Etter [15] presented a description of the topology of hydrogen bonds in crystalline hydrates.

#### Hydrates IV – polymorphs of ice

The pure form of hydrate can be considered water in the solid phase, *i.e.* ice, where there is no guest hydrated molecule and the structure is stabilized by hydrogen bonds formed between water molecules. About 17 ice polymorphs are currently known. Their stabilities obviously depend on pressure and temperature. The most typical form of ice which exists on the surface of the Earth is the *I<sub>h</sub>* polymorph - a hexagonal form characterized by disorder of the hydrogen atoms of H<sub>2</sub>O molecules in the crystal lattice. When the temperature decreases, the disorder changes from dynamic to static. Therefore, even at temperatures close to 0 K, the orientation of the water molecules is random and the structure shows some redundant entropy [16]. It is, however, possible to obtain an ordered form of the ice *I<sub>h</sub>* polymorph by crystallizing highly diluted aqueous KOH solutions [17]. This form of ice created by doping is called the *XI* polymorph. Very interesting

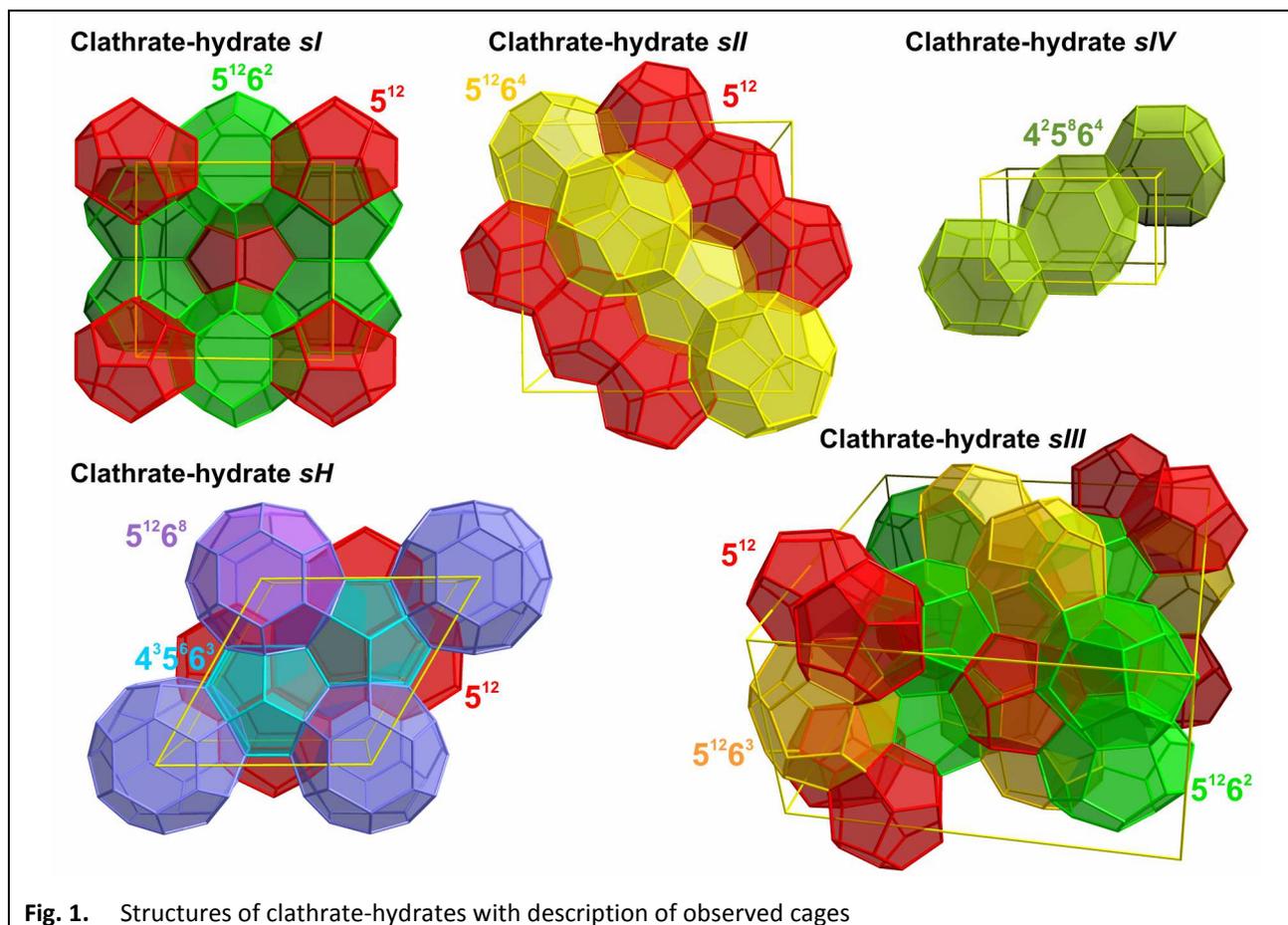
metastable ice polymorphic systems recently discovered were obtained by the slow evacuation of gas molecules (neon [18] or hydrogen [19]) from hydrate clathrate structures, leading to polymorphs *XVI* or *XVII*, respectively. Ice structures which exist at atmospheric pressure contain a relatively large amount of free space, and the density of their crystals are below  $1 \text{ g}\cdot\text{cm}^{-3}$ . The water molecules are therefore less efficiently packed in the solid phase than in the liquid phase.

### Hydrates V – clathrate-hydrates

Another extremely important group of hydrates worth highlighting are the clathrate-hydrates mentioned above in the context of new crystalline forms of ice formation. These are crystalline systems where water molecules connected by hydrogen bonds form a three-dimensional network and each of the molecules is surrounded by four neighbouring  $\text{H}_2\text{O}$  molecules, as is the case in ice polymorphs. However, in hydrate clathrate structures, there are rather large open voids that can accommodate hydrophobic molecules. Since the hydrogen bonds around the water molecules are already saturated, the hydrated molecule is not stabilized by hydrogen bonds. The clathrate molecules filling these spaces are highly disordered and adopt many alternative positions in the voids. These hydrate clathrates are host-guest systems and a particularly important group of such hydrates are clathrates of methane (or natural gas) naturally occurring in nature. They form deposits in sediments of the continental shelf (for example in the Gulf of Mexico) or accompanying deposits of hydrocarbons (for example in Siberia). It has been estimated that the methane content in such hydrated clathrates may exceed the classical resources which accompany the oil deposits [20].

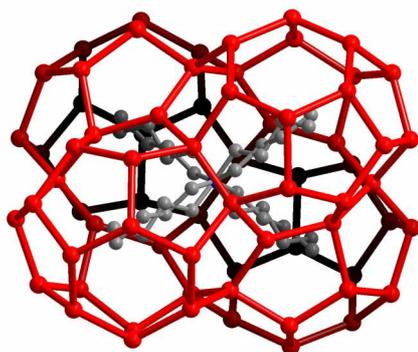
There are several types of clathrates that differ by symmetry, the size of the unit cell, and the number and type of voids in the crystal lattice [21,22]. The most popular are clathrate-hydrates of *sI*, *sII* or *sH* type [20,23]. It is worth mentioning rather exotic *sIII* bromine clathrate [24] or *sIV* argon clathrate [25], the latter stable under elevated pressure. The structures of these clathrates are presented in **Figure 1**. Cages in clathrate-hydrates that are, in fact, polyhedra with oxygen atoms in the corners are described by giving the type and number of polygons constituting its faces. For example: the notation  $5^{12}$  refers to a cage which is formed by twelve pentagons. Ideally, this cage has the shape of a regular dodecahedron. In clathrate-hydrates, methane molecules occupy smaller cages, while the higher analogues occupy larger ones. It may also happen that larger cages are occupied by several methane molecules. The methane clathrates discussed here are not stable at ambient pressure and decompose into methane and water at room temperature. Higher pressure is required for their stabilization. For this reason, methane hydrates can be a serious problem in the oil industry. If some moisture with natural gas being under an increased pressure gets into the gas pipeline, clathrate-hydrates may crystallize, blocking the gas flow. Substantial effort has therefore been directed into research on inhibition of crystallization in these types of systems.

Not only hydrocarbons can crystallize in the form of clathrate-hydrates. There are also structures containing  $\text{Cl}_2$  molecules and the previously mentioned systems with  $\text{Br}_2$  or  $\text{CO}_2$ . The first documented synthesis of hydrate was carried out by Sir Humphry Davy, who obtained a chlorine clathrate in the 19<sup>th</sup> century [26,27]. It is also worth mentioning that research on hydrates of  $\text{CO}_2$



was led by Zygmunt Wróblewski [28] also a long time ago. Clathrate-hydrates are host-guest systems where ideally no hydrogen bonds (not even weak ones) exist between the hydrated molecule and the surrounding H<sub>2</sub>O molecules. Water-rich hydrates, especially of aliphatic amines, where the amino group forms strong hydrogen bonds with water (an example of which is the structure of *n*-propylamine 6½ hydrate [13] mentioned in **group III** of hydrates) are called semiclathrate-hydrates [29]. Although the name suggests that such hydrates are similar to clathrates, in fact they are not ideal host-guest inclusion structures. Semiclathrates are also called hydrates containing per-alkylated ammonium, phosphonium, sulfonium salts of halides, carboxylates, OH<sup>-</sup>, or even tungstates [30-37]. However, these are structures stabilized by additional ionic interactions and, in contrast to classical gas clathrates, they show enhanced thermal stability. The melting points of such crystals often exceed dozens of degrees Celsius. The relatively small anions F<sup>-</sup>, OH<sup>-</sup>, Cl<sup>-</sup> and Br<sup>-</sup> are incorporated into a three-dimensional network of water molecules, and in the case of smaller individuals, such a framework shows a substitution disorder. Larger anions, like carboxylates, interact with water molecules to form hydrogen bonds with the COO<sup>-</sup> fragment. Hydrophobic organic cations occupy rather large voids which closely resemble the joined cages observed in clathrate-hydrates, as shown in **Figure 2** taking the structure of tetrabutylammonium fluoride as an example [38]. In the hydrate structures of **group III, IV** or **V**, the typical contact length of O...O is approx. 2.7 Å at ambient pressure. In the case of disordered structures or those containing guest ions in the water framework, this distance may be significantly different.

Concerning non-ionic semiclathrates, these systems are observed in the group of the water-rich



**Fig. 2.** Cage in structure of tetrabutylamine fluoride [38] occupied by the cation.

hydrates of aliphatic amines, such as *n*-propylamine [13], diethylamine [39] *etc.* The only exception is the  $9\frac{3}{4}$  hydrate of *tert*-butylamine [40,41] where the water molecules create an unprecedented three-dimensional framework with an amine molecule occupying the  $4^35^96^27^3$  cages, whereas the  $7\frac{1}{4}$  hydrate of this compound [42] does not form a clathrate structure. In turn, the multi-component system containing water, *tert*-butylamine  $H_2S$  and Xe

forms a similar architecture to hydrate clathrate of type *sII* but the entire framework of water molecules (not only hydrogen atoms but also oxygen atoms) is disordered and there are weak amine-water hydrogen bond interactions in the structure [43]. Therefore, this is not a classic host-guest system. This raises an important question: what types of hydrates can be created for a given guest molecule or one having a similar shape, size and/or nature.

### Hydrates VI - water very weakly interacting with the structure

To complete the general description of hydrates, it is worth mentioning systems where the water is extremely weakly involved and does not play any significant structural role. Firstly, we can imagine water adsorbed on a surface - its amount will depend on the ambient humidity. At this level of generality, we can also consider a hydrate sponge which, after drying, becomes an anhydride and its skeleton/structure is not destroyed. An analog of such a sponge in material chemistry is MOF (Metal Organic Framework) type systems [44] which, having a porous structure, are also extremely durable and can create sizable monocrystals. In these pores, depending on the air humidity, the water present in the MOF crystal structure may be adsorbed in a highly disordered way. Heating or changing the environment obviously releases weakly bound water molecules from the porous material.

### Aims of the research

The classification of hydrates into groups given in the introduction part of this presentation is obviously subjective. However, it demonstrates the great variety of such systems and allows more precise definition of the research problem and more comprehensive presentation of the published research results, which are the basis for this habilitation work.

First of all, the research presented here refers to the crystallization and understanding of the exact crystal structure of hydrates, mainly **groups III** and **V** of selected organic compounds having small molecular size. The investigated compounds are *tert*-butylamine, tetrahydrofuran (THF), pyrrolidine, *tert*-butanol, cyclobutylamine and piperidine. The aim of the research is to determine whether, what type and how many hydrates can be formed by the compounds in question. Moreover, an important research question concern whether single hydrates having a stable, well-defined phase independent of dilution are formed by a given system, or perhaps the reverse - the molecules tend to create many hydrates with different architectures. In particular, for

*tert*-butylamine it is important to find out whether it forms host-guest system(s) or, as in the case of other known amine hydrates, the organic molecule interacts with H<sub>2</sub>O molecules through well-defined hydrogen bonds. Furthermore, does the change of the functional group in *tert*-butylamine from amino to hydroxyl significantly affect the nature of the hydrates (the compounds are isoelectronic)? Another problem arises: to what extent has the order of the amino group impact on the type of molecular architecture? And last but not least: what are the characteristics of the architecture(s) formed by pure organic compound in the absence of the water molecules in the crystal lattice?

The types of systems analyzed, especially if they contain many water molecules, can show disorder particularly in the hydrophobic fragments of molecules weakly interacting with the water. Such disorder is frequently observed, especially in clathrate-hydrate. The use of a correct disorder model in the crystallographic solution procedure can significantly improve the quality of the resulting structural data and reduce discrepancy factors to a reasonable level. A low structural refinement error is of course a relative term. For a protein crystallographer, an error at the level of 20% may be small, while a ten-times lower value for the trivial structure of sodium chloride is considered to be very high.

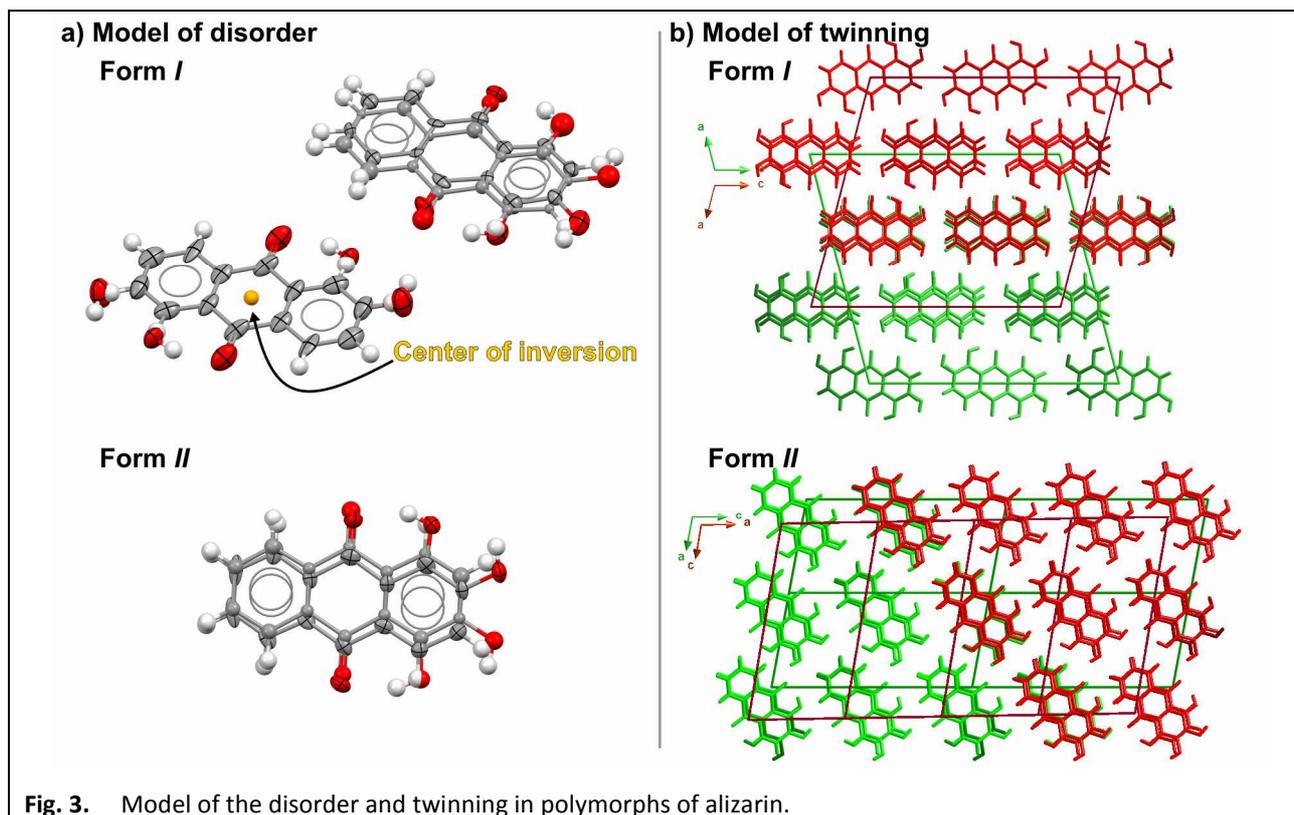
In order to better show the discussed effect on the final structures, the results are presented also taking into account disordered structures of polymorphs of alizarin and 4,4'-bipiperidinium chloride hydrate. On the other hand, the author also discusses a perfectly ordered structure of polymorphs containing DMANH<sup>+</sup> and H<sub>5</sub>O<sub>2</sub><sup>+</sup> cations compensated by the presence of chloride anions for which the quality of the obtained data allowed analysis of the electron density distribution (EDD) in the crystals.

The numbering of the papers which are considered to make up the habilitation achievement from **H1** to **H8** is arranged chronologically following the dates of their publication. In the "**Results**" chapter, these papers are discussed in a sequence which provides a more consistent description of the achievement. This leads to the following order: **H7**, **H3**, **H8**, **H6**, **H5**, **H2**, **H4** and **H1**.

## Results

### Disorder in polymorphs of alizarin [H7]

Alizarin is a popular natural anthraquinone dye known already in ancient times. It is obtained from the roots of *Rubia tinctorum*. The crystalline structure of this simple compound was determined in the 1960s [45] and confirmed in 2005 [46]. However, the relatively high reported discrepancy factors of the structure refinements is a warning sign. The earlier work ( $R1 = 26\%$ ) may be associated with quite old and imprecise measurement procedures. In the second case ( $R1 = 20\%$ ) there may have been problems with the structure refinement. Often, these can be observed for twins, intergrowths, highly disordered, modulated or domain-type structures. Structural studies carried out for crystals obtained by sublimation (*i.e.* an analogous method as described in reference 46) have shown that their structure is disordered. In addition, the crystals are twinned. Refinement of the structure using both twin domains and appropriate modelling of the disorder in the centrosymmetric  $P2_1/c$  space group led to a final discrepancy factor  $R1$  not exceeding 7%. Interestingly, the slow crystallization of alizarin from saturated toluene solution led to a new



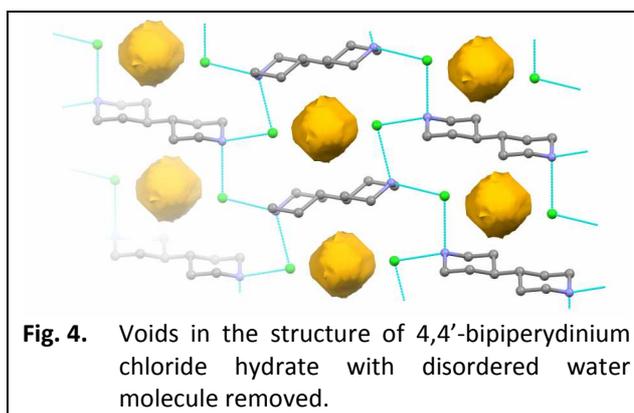
**Fig. 3.** Model of the disorder and twinning in polymorphs of alizarin.

polymorph (II) of this dye. These crystals are also twinned and contain disordered organic molecules in the crystal lattice. In this case, the final discrepancy factor is  $R1 = 4.21\%$  and thus, along with fully acceptable other parameters, can satisfy even the most demanding crystallographers. Crystals of the form II belong to the noncentrosymmetric space group  $Pa$ . In polymorph I, the asymmetric part of the unit cell contains one molecule located in a general position but disordered into two alternative sites with refined occupancy ratio of 0.611(5):0.389(5) and half of the second, also disordered, moiety positioned on the centre of inversion. As the alizarin molecule does not have this element of symmetry, the obtained model corresponds to a crystal with randomly oriented molecules. In polymorph II there is only one type of molecule which is disordered over two alternative sites with a refined occupancy ratio of 0.771(4):0.229(4), all located in a general positions. The disorder model of the molecules for both polymorphs is shown in **Figure 3 a)** while the twinning with possible domain orientations is presented in **Figure 3 b).**

### Disorder in crystals of 4,4'-bipiperidinium chloride 0.12 hydrate [H3]

Another example of a disordered structure is the non-stoichiometric hydrate of 4,4'-bipiperidinium chloride. In this case, however, this effect when overlooked or simply not included during the structure refinement does not have such a large impact on the final result as in case of alizarin polymorphs. This is an example of a hydrated salt belonging to the **group III** described in the introduction. The 4,4'-bipiperidine molecule can be treated as a saturated analogue of 4,4'-bipyridine - a relatively popular building block used in crystal engineering [47] both in its neutral and ionic forms [48]. This is facilitated by an essential change in the nature of pyridine fragments, which in the neutral molecule are perfect ligands; whereas after protonation they become donors in hydrogen-bonded systems. The 4,4'-bipiperidine molecule in crystal structures

appears much less frequently and mainly in the dication form. The aliphatic character of this secondary amine and the larger size obviously affects the nature of interactions in crystals where, unlike 4,4'-bipyridine, it will not participate in interactions of the  $\pi$ - $\pi$  type. Crystallization of HCl-acidified aqueous solution of 4,4'-bipiperidinium chloride yielded hitherto unknown crystals containing 4,4'-bipiperidinium



**Fig. 4.** Voids in the structure of 4,4'-bipiperidinium chloride hydrate with disordered water molecule removed.

dications and chloride anions. The final  $R1$  discrepancy factor of the structure was 3.98%, thus corresponding to a reasonably well-refined structure. However some concern appeared after analysis of the residual maximum and minimum electron density in the crystal ( $0.70 \text{ e}\text{\AA}^{-3}$  and  $-0.29 \text{ e}\text{\AA}^{-3}$ , respectively). Due to the presence of an atom with a relatively high electron density, these values and even their ratio are acceptable. However, following a careful analysis of the structure, some doubts arise. In the crystal, chloride anions interacting with amino groups *via* hydrogen bonds form layers with the cations. In these layers between organic moieties there are voids with approximate volumes of  $18 \text{ \AA}^3$ . This is visible in **Figure 4**. The volume of the voids in the crystal lattice has been calculated using the Mercury software [49]. In the unit cell there are four such voids. The above-mentioned residual electron density maxima are located in the middle of each empty space. It is quite reasonable that, in this area, a molecule with partial occupancy could be located. Due to the proximity of chloride anions, this molecule is most likely a water molecule. The refined occupancy of this molecule yielded 0.12(1) and this overall amount of non-stoichiometric number of water molecules is present in the unit cell. The structural model which included such disordered and partial occupancy  $\text{H}_2\text{O}$  molecule led to a slightly better discrepancy factor of  $R1 = 0.0359$  together with lower residua of electron density of  $0.36 \text{ e}\text{\AA}^{-3}$  and  $-0.29 \text{ e}\text{\AA}^{-3}$ . The disordered water molecule is located on the  $2/m$  site symmetry between the chloride anions and the aliphatic rings of the cation. The small amount and disorder of the  $\text{H}_2\text{O}$  moiety is due to its unfavourable position. This structure can be treated as a kind of reverse clathrate where the  $\text{H}_2\text{O}$  molecule is located in the gaps. In the case of an aromatic analogue of the investigated compound, *i.e.* 4,4'-bipyridine, a stoichiometric monocationic chloride dihydrate with proton disorder at the heteroatom is known [50].

### Neutron diffraction and charge density analysis in polymorphs of 1,8-bis(dimethylamino)naphthalene hydrochloride hydrates [H8]

In context of the previously presented disordered structures of alizarin and 4,4'-bipiperidinium chloride hydrate, it is desirable to present exemplary structures of fully ordered crystals. This can be based on two polymorphs containing 1,8-bis(dimethylammonium)naphthalene cations, chloride anions and Zundel-type  $\text{H}_5\text{O}_2^+$  moieties; so these systems, according to the classifications given in the introduction, belong to hydrates of the **Ila group**. The native 1,8-bis(dimethylamino)naphthalene molecule referred to as DMAN is also called the proton sponge [51-53]. This diamine, which is a strong base, protonates very easily with the " $\text{H}^+$ " ion located between

amine groups where it is stabilized by the electron lone pairs of the nitrogen atoms forming a  $\text{DMANH}^+$  cation. During the crystallization of the HCl acidified amine solution in water, good quality crystals of hydrates were formed relatively quickly. In total, four crystalline phases can be described for the  $\text{DMANH}^+\text{-Cl}^-\text{-H}_2\text{O}$  system [6]. Only two of these phases have ordered structures. They contain  $\text{H}_5\text{O}_2^+$  ions that differ in symmetry. In a monoclinic polymorph (*M*), this cation occupies a general position, while in the triclinic form (*T*) there are two crystallographically independent ions with  $\bar{1}$  symmetry and protons lying exactly between water molecules. The crystals of both polymorphs are not only rapidly-growing species. Within a few minutes, individual crystals suitable for high-resolution X-ray diffraction measurements could be obtained, even reaching sizes up to several millimetres. This was especially evident for the *M* polymorph. For this form, apart from the high-resolution measurement, it was also possible to conduct a neutron diffraction experiment at the ISIS Neutron and Muon Source in Chilton (UK). In spite of the ionic interactions the crystals have limited thermal stability. Both polymorphs easily decomposed when removed from the mother liquid. During the experiments it was necessary to use an appropriate oil that allowed the crystal selection and manipulation, especially during preparation of the neutron diffraction measurement. From this type of experiment, information on the precise positions of hydrogen atoms in the crystal lattice can be obtained. This, together with high resolution X-ray diffraction experiments, makes it possible to go beyond the classical model of spherical atoms during the structure refinement routinely used in crystallography [54] and to use the more advanced multipole model [55].

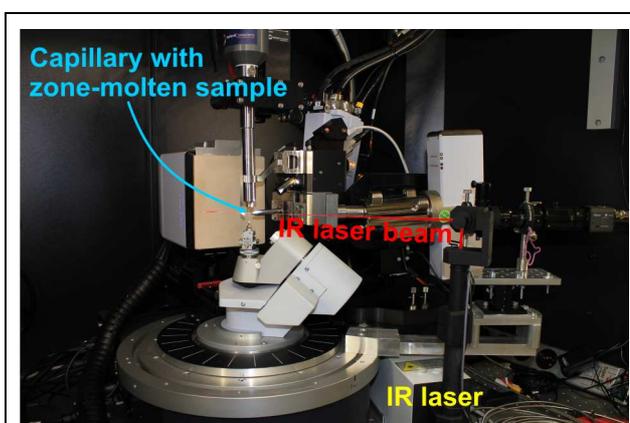
The use isolated spherical atoms in the case of high-angle X-ray measurements can bring surprising results. Although classical refinement of the structure for the polymorph *M* with the  $2\theta$  angle range to up to  $110^\circ$  ( $d = 0.43 \text{ \AA}$ ) gave a low final discrepancy factor  $R1 = 3.21\%$ , the electron density residua are very large ( $+1.1 \text{ e\AA}^{-3}$ ,  $-0.58 \text{ e\AA}^{-3}$ ). The strongest maxima appeared in the vicinity of  $\text{Cl}^-$  ions, *i.e.* the relatively highest electron density and on C-C/C-N bonds in the  $\text{DMANH}^+$  ion. For the high resolution data the application of the multipole model enables a precise distribution of electron density in the crystal that includes charge transfer between atoms and improved structure refinement parameters. Of course, the approach presented here can be applied for the crystals without defects, which has an ordered structure and gives intense reflections even at high diffraction angles. However it is also possible to apply a multipole model to partially disordered systems [56]. For a standard diffraction measurement, the required data resolution is approx.  $0.83 \text{ \AA}$ , although for extremely disordered and weakly diffracting crystals sometimes even this value may be impossible to achieve.

### ***tert*-Butylamine hydrates [H6] and applied methodology of crystallization of liquids**

The crystals discussed in the previous subsections were obtained by sublimation or typical crystallization by standard slow evaporation of a solution of solid substances at room temperature. The other compounds - aliphatic amines or THF - are low boiling liquids, while *tert*-butanol melts at approx.  $25^\circ\text{C}$ . The mixtures of these compounds with water are liquids and under cooling at appropriate low temperatures they solidify, creating microcrystalline powders or amorphous glass phases. To determine the crystal structures either of the pure phase or of its

hydrates, it is necessary to have good quality crystals, preferably single crystal. For systems with limited thermal stability, a special crystallization procedure must be applied directly at the goniometer of a diffractometer to avoid troublesome handling with unstable crystals. Such a procedure was invented by Roland Boese, University of Duisburg-Essen. It is based on the zone melting method [57,58]. A thin-walled glass capillary containing the liquid is placed on a goniometer of a single crystal diffractometer and cooled with a stream of cold nitrogen from a low-temperature device. At low temperature, the liquid solidifies. Then, the resulting solid is locally heated by a beam focused on the capillary using an IR laser installed in the diffractometer enclosure. The choice of the power of the laser and proper beam control (which moves along the capillary) allows one to obtain good quality crystals suitable for diffraction measurement. The *in situ* crystallization device is installed on the Bruker D8 Venture diffractometer as shown in **Figure 5**. This equipment is placed in the Jan Czocharlski Advanced Crystal Engineering Laboratory of the Faculty of Chemistry at the University of Warsaw. It was purchased as part of the apparatus grant received from the Fund of Science and Technology of the Polish Ministry of Science and Higher Education (614/FNiTP/115/2011). This is the first installation of this type on the D8 Venture diffractometer. I personally made the adaptation of this device for performing *in situ* crystallization experiments. A complementary methodology for structural investigations of compounds that are liquids gives high-pressure crystallography [59]. My research has focused on experiments performed at ambient pressure but at lower temperatures.

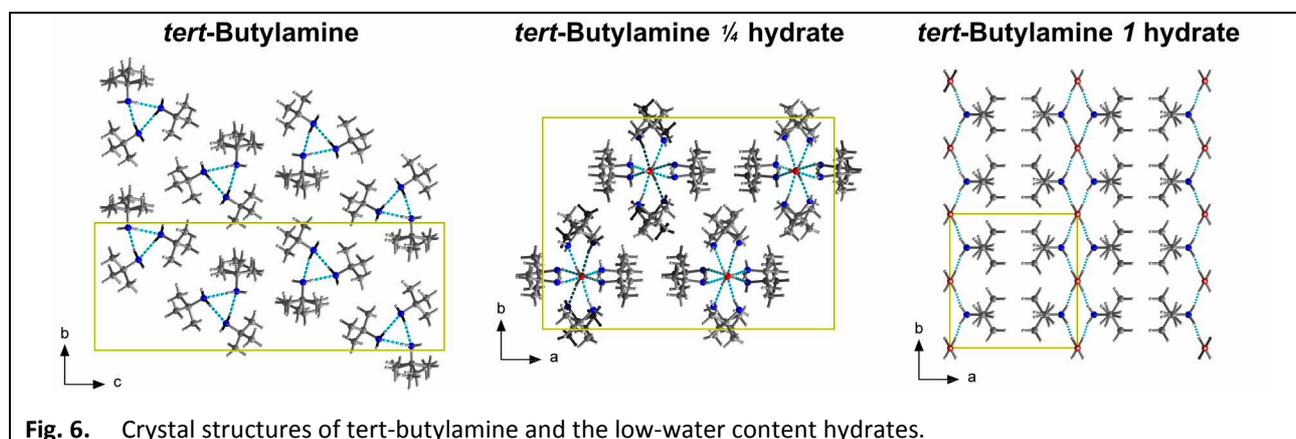
In the case of structural studies of *tert*-butylamine and its hydrates, most of the experiments were carried out during my postdoctoral fellowship in the group of prof. Roland Boese at the University of Duisburg-Essen in Essen, Germany. The equipment used in the studies was different from the one presented in **Figure 5**. For two-component amine-water systems, two hydrates were already known, although based on phase diagram analysis [60] a larger number could be expected. One is the  $7\frac{1}{4}$  hydrate [42]; another contains  $9\frac{3}{4}$  water molecules per amine molecule, a system which has been considered to be clathrate-hydrate [40,41]. The refinement error (*R*) of both these structures is, however, relatively high and equals to 11.5% and 8.8%, respectively. The results of the experiments presented in the **H6** paper concerning systematic studies of crystallization, depending on different molar ratios of the components, gave 7 hydrates and the structure of the neat amine. This compound is therefore an example of the most frequently hydrated, neutral organic molecule forming hydrates with a stoichiometric composition. The neat amine is a compound with a relatively low melting point of just over 203 K. The unit cell of the amine crystals contains three symmetrically independent molecules. One of the molecules displays disorder of the *tert*-butyl fragment. In the crystal lattice, the molecules interact by N-H...N hydrogen bonds. They are arranged in a



**Fig. 5.** IR laser used for the *in situ* crystallization installed on the D8 Venture diffractometer in the Jan Czocharlski Advanced Crystal Engineering Laboratory of the Faculty of Chemistry at the University of Warsaw.

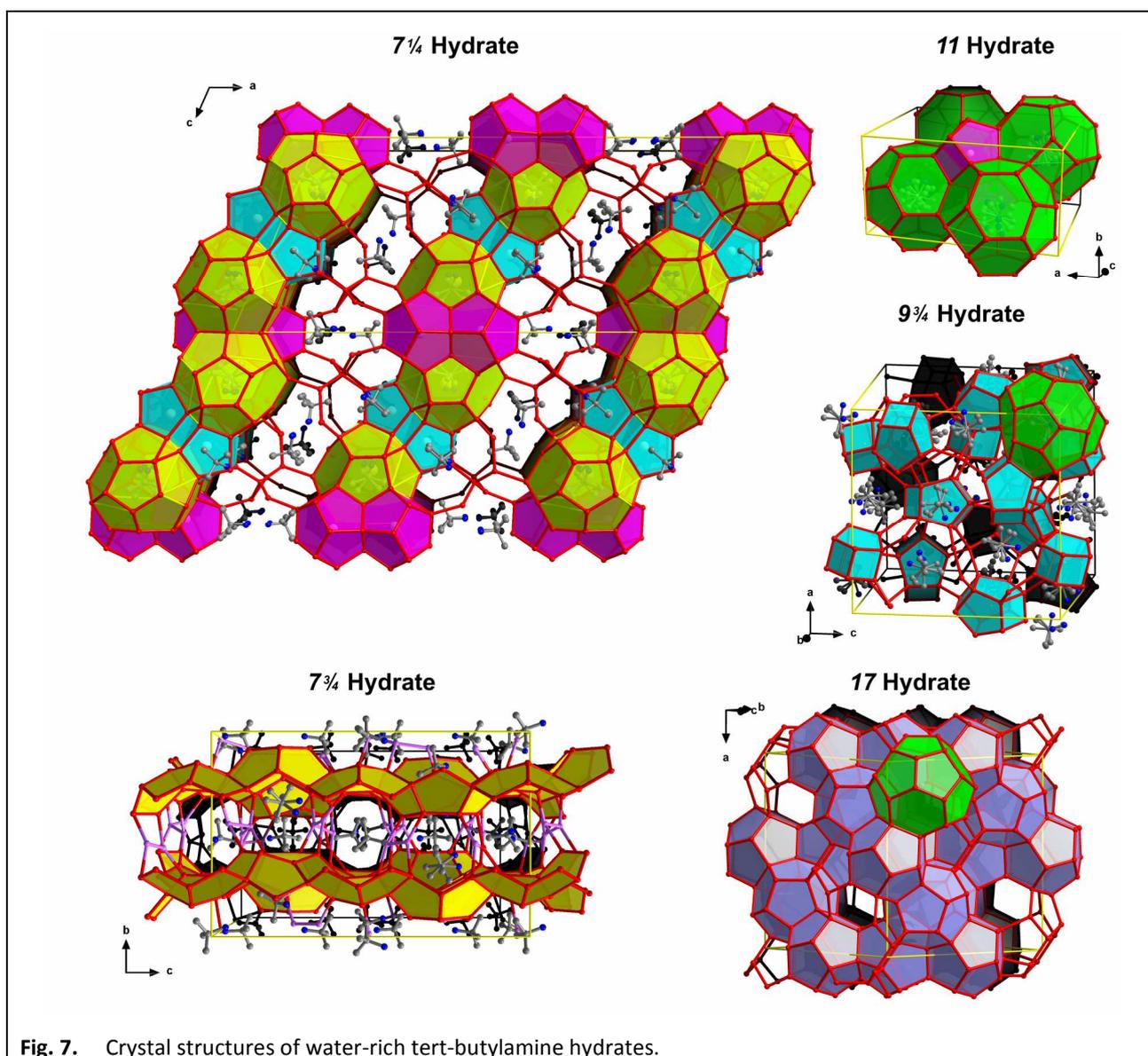
way to form helices. Importantly, only one of the hydrogen atoms of  $\text{NH}_2$  groups is involved in the hydrogen bond. The helices are arranged along the direction  $[100]$ . The first amine hydrate is a system containing one molecule of water surrounded by four molecules of the amine. This structure is fully ordered with well-defined positions of all atoms, also including hydrogens. The  $\text{H}_2\text{O}$  molecule interacts with amino groups, playing the role both of donor and acceptor of hydrogen bonds. There are additional hydrogen bonds between the amino groups linking the molecules to the columns. Crystallization with a higher water content gives the monohydrate where  $\text{H}_2\text{O}$  molecules have disordered hydrogen atoms. They bind the amine molecules to form layers. The structures of the three compounds discussed are shown in **Figure 6**.

Another possible system is the already known  $7\frac{1}{4}$  hydrate. In this structure, the water molecules form layers with amine molecules that are involved in strong  $\text{N-H}\dots\text{O}$  hydrogen bonds. The layers are bound by  $\text{H}_2\text{O}$  molecules located between them, stabilizing the amine molecules. The structure is very complicated and contains eight molecules of amine and 58 molecules of water in the independent part of the unit cell. The hydrogen atoms of amino groups and of water molecules are disordered. In this case, it is analogous to the structure of the ice polymorph  $I_h$  or  $I_c$ . Including the disorder of H atoms in the model (the objects with very low electron density) allowed me to obtain a final error of refinement at the level of 7%. Surprisingly, for an only slightly higher water content, the amine forms a  $7\frac{3}{4}$  hydrate which displays a completely different topology. In this structure  $4^45^4$  and  $3^35^6$  cages can be found, which are too small to accommodate the amine molecule. These molecules are located in canals or layers in a three-dimensional framework of water. This framework is disordered and some of the water molecules occupy alternative positions. In the structure, it is possible to distinguish significantly large, irregular and concave cages of the type  $4^{15}10^6$  filled by an amine. In fact, the cages are not fully closed (this impression results from the averaging of the disordered structure). Hydrogen bonds are formed between the water molecules and the amines. A careful analysis of the architecture of next  $9\frac{3}{4}$  *tert*-butylamine hydrate revealed that all water molecules forming a three-dimensional network are disordered. This disorder is manifested by the alternative positions of oxygen atoms whose occupancy is up to 10%. The alternative positions of oxygen atoms are located in close proximity of the positions defined for the perfect clathrate. The disorder of the water molecules' framework indicates the presence of host-guest interactions in the structure of the discussed hydrate. Therefore, strictly it is not a clathrate. Considering this disorder, the final  $R1$  factor for this



structure is at the level of 5.2%. In the structure of this hydrate, for the ordered model, two types of cages can be distinguished – an empty  $4^45^4$  one and the cage occupied by a disordered amine of type  $4^35^96^27^3$ . The structure of another hydrate containing 11 molecules of water, although at first glance also seems to be typical of clathrate-hydrate, is in fact disordered. Amine molecules occupy large cages of type  $4^15^{10}6^6$  (analogously to  $7\frac{3}{4}$  hydrate), whereas small cages of  $4^35^6$  are empty. The water molecules' framework in this structure is also disordered with alternative positions of oxygen atoms with occupation factors in some cases exceeding 10%.

The last structure containing water observed for *tert*-butylamine is **17** hydrate. The framework built of water molecules corresponds to the *sII* clathrate, but H<sub>2</sub>O molecules show a disorder similar to  $9\frac{3}{4}$  and **11** hydrates. Amine molecules occupy large gaps, while  $5^{12}$  cages remain empty. In this structure, due to the huge disorder of the organic molecule, it was not possible to locate the amino group. However, due to the probability of the presence of hydrogen bonds between amine and water molecules, this system is not considered to be a clathrate-hydrate, similarly as the other water-rich *tert*-butylamine hydrates. The structures of amine hydrates with high numbers of water molecules are presented in **Figure 7**. The figure shows an ordered model of a



**Fig. 7.** Crystal structures of water-rich *tert*-butylamine hydrates.

network of water molecules. The H<sub>2</sub>O molecular framework corresponding to the ordered model in **9** and **11** *tert*-butylamine hydrates appears in ionic **8** and **10** hydrates of tetramethylammonium hydroxide [61, 62]. In these systems, OH<sup>-</sup> anions are incorporated in the network of water molecules, so the network is no longer molecularly homogeneous, while hydrophobic cations occupy cages.

The quality of crystals obtained during the *in situ* crystallization process depends on the nature of intermolecular interactions but also on the duration of the entire process. It is rather obvious that the longer the crystallization takes, the bigger crystals can be obtained. It may however happen that, even after a few hours of the process, an oligocrystal in the form of multiple needles is obtained. Another problem concerning the use of this experimental technique is the necessity of performing crystallization of substances in the capillary which can cause angular limitations during the diffraction measurement, resulting in lower completeness of the collected reflections. This is a particularly important problem for crystals with low symmetry. For the crystals of *tert*-butylamine and its hydrates, the completeness of the data varies from less than 83% for **11** hydrate to almost 100% for hydrates crystallizing in a cubic system. Almost full completeness of data for the low-symmetric monoclinic **7** hydrate results from the experiment conducted on a more advanced and dedicated to *in situ* crystallization D8 Venture diffractometer. In the case of the **4** hydrate, the crystals were very small and scattered the X-ray radiation to a relatively low  $2\theta$  angle slightly above 40° ( $d = 1.03 \text{ \AA}$ ).

### THF clathrate-hydrate [H5]

Depending on the water content, *tert*-butylamine forms a whole series of hydrates. The structure with the highest number of H<sub>2</sub>O molecules, *i.e.* **17** hydrate, corresponds to a structure of the clathrate-hydrate of type *sII*, however has a disordered network of water molecules. It is known that THF also forms *sII* clathrate [63,64] where the molecular ratio THF to H<sub>2</sub>O is equal to 17 as well. However, there is no precise structural data for this system thus it is difficult to analyse potential host-guest interactions or confirm if the water framework is ordered in the crystal lattice. Crystallization of the THF-water mixture at 220 K gave a single crystal. In the finally refined structure, the disordered THF moieties occupied large cages while the oxygen atoms of the water molecules were ordered. There were no typical hydrogen bonds THF...H<sub>2</sub>O. It is, therefore, the structure of typical clathrate-hydrate. Hydrogen atoms of water molecules were disordered over two alternative positions. For such a relatively simple structure and unsophisticated disorder model, the final discrepancy factor was an 4.3%. The final structure of the THF clathrate-hydrate is shown in **Figure 8**. The crystals of this system are relatively stable - they melt at approx. +5°C and, most interestingly, crystallize very easily from solutions with a wide range of THF concentrations. We use this inherent property of THF-water mixture while conducting

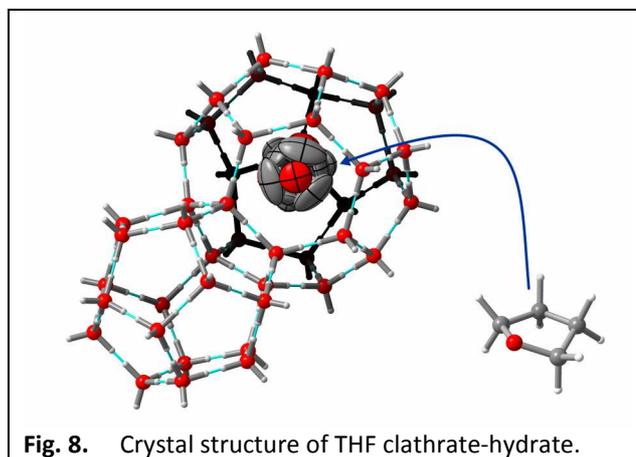


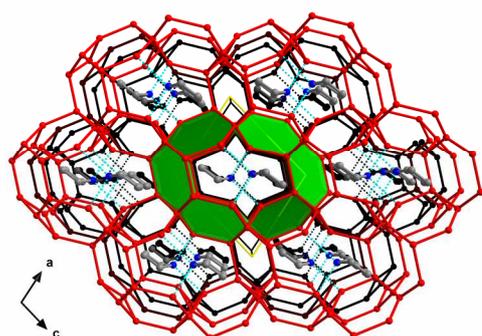
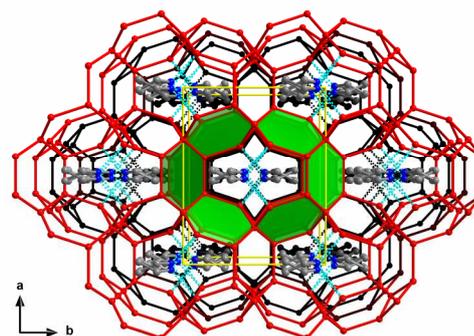
Fig. 8. Crystal structure of THF clathrate-hydrate.

crystallography classes for the students in their first level studies at the Faculty of Chemistry of the University of Warsaw. During such classes, it is possible to obtain single THF clathrate hydrate crystals within a dozen or so minutes and complete diffraction measurements in the next several minutes. Thus, as it can be seen, unlike *tert*-butylamine, THF forms only one hydrate which is also a true clathrate-hydrate.

### **Pyrrolidone and hydrates [H5]**

A compound exhibiting similarity to THF, but of course with completely different properties, is pyrrolidine. Instead of the ether oxygen in the ring it has the NH group. The structure of this amine was already known both under ambient [65] and higher pressure [66]. Crystallization experiments and diffraction measurements carried out for the rapidly solidified pyrrolidine in a capillary at  $T = 180$  K on a powder diffractometer verified that a new crystal phase had been formed. This phase slowly transformed to the known low temperature (*LT*) polymorph. Performing the *in situ* crystallization on a single crystal diffractometer at  $T = 207$  K (near melting point) confirmed the presence of a high temperature (*HT*) amine polymorph. Analogously to the *LT* form, in the *HT* variant, the molecules interact with each other by N-H...N hydrogen bonds and are arranged in columns. The fully reversible phase transition of  $HT \leftrightarrow LT$  is related to the reorientation of these columns and the simultaneous change of symmetry  $Pbca \leftrightarrow P2_1/c$ . Lowering the symmetry while cooling resulted in twinning of the crystals. Both forms adopted very wide range of temperature stability. On cooling, the *HT* polymorph transformed into the *LT* form at 165 K, while the *LT* phase was preserved up to 205 K (the melting point of the pyrrolidine is 210 K). In the case of interactions with water of this secondary amine, it is expected that a hemihydrate with a water molecule linking two molecules of pyrrolidine through the O-H...N hydrogen bonds is formed. The mixture with such proportions of both compounds undergoes vitrification at low temperature. Only by heating the mixture with an IR laser beam facilitated the formation of a powder form. Then larger crystals could be obtained by slow crystallization. The resulting phase was actually a hemihydrate with the expected molecular architecture.

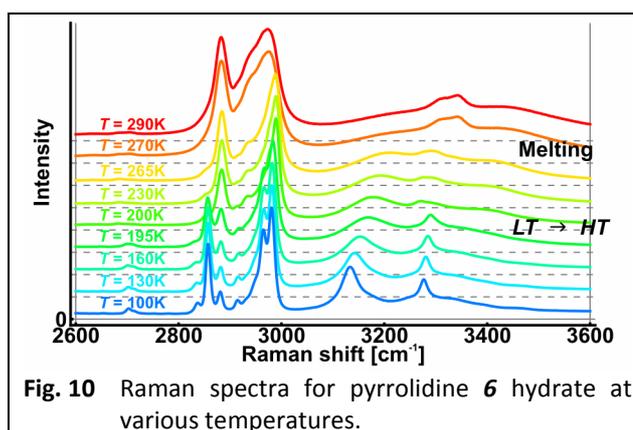
Pyrrolidine creates one more system with water. It is a hexahydrate and crystallizes from a mixture containing amine and water in a rather wide range of molar ratios from 1:3 to even 1:9. Hexahydrate crystals, like neat amines, exhibit an enantiotropic polymorphism. When cooled, the orthorhombic *HT* phase transforms to a monoclinic *LT* variant. During the phase transition associated with the loss of orthogonality of the crystallographic system, the crystals became twinned. The transformation was reversible and displayed hysteresis typical for transitions of the first type. DSC measurements carried out for a mixture of water and amine in a molar ratio of 1:6 indicated that, when cooled, the transition temperature was 190 K, while heating it became 196 K. Hexahydrate crystals melt at about 269 K. The structure of the hexahydrate is composed of a three-dimensional network of water molecules, where the channels are occupied by amine species which form N-H...O hydrogen bonds with H<sub>2</sub>O molecules. In the *HT* phase, the amine moieties and the hydrogen atoms of the water molecules are disordered. In the *LT* polymorph, the entire structure becomes ordered including the positions of the hydrogen atoms of H<sub>2</sub>O molecules. A comparison of the structures of both polymorphs is shown in **Figure 9**. For the *LT*

Pyrrolidine hexahydrate, form *LT*  $T=100\text{K}$ Pyrrolidine hexahydrate, form *HT*  $T=210\text{K}$ 

**Fig. 9.** Comparison of the *LT* and *HT* polymorphs of the pyrrolidine hexahydrate.

phase, it is clearly seen that the amine molecule forms two types of hydrogen bonds with the neighbouring water species. In the case where the amino group is the hydrogen bond acceptor, the bond is stronger (shorter O...N distance) as compared with the situation when it plays a role of a donor. In the *HT* phase, these contacts are, of course, averaged due to the disorder.

The dynamics of molecules in crystals can be investigated with use of spectroscopic techniques. The diffractometer on which the crystallization of pyrrolidine hexahydrate has been carried out is coupled with a Raman spectrometer. Raman spectra were recorded for crystals obtained at different temperatures. They show the changes in the structure during the phase transition in the solid phase but also during melting. These spectra for the frequency range of stretching vibrations of C-H, O-H and N-H types are given in **Figure 10**. It is clear that, at  $T = 100\text{ K}$ , the vibration bands OH ( $\nu = 3134\text{ cm}^{-1}$ ) and NH ( $\nu = 3277\text{ cm}^{-1}$ ) of the molecules involved in the hydrogen-amine hydrogen bond are relatively sharp and intense. As the temperature rises, these bands are shifted towards higher frequencies and become broader. This is particularly well observed for the O-H vibrations. At the *LT*→*HT* phase transition, the changes are more discrete, similar to during melting. Coupling the Raman spectra with X-ray diffraction experiments allows us to follow structural changes and also to determine the phase transition temperatures. In the case of hexahydrate pyrrolidine, close to its melting point the oxygen atoms of water molecules are also disordered and the Raman spectrum loses its fine structure, resembling the spectrum of the liquid.

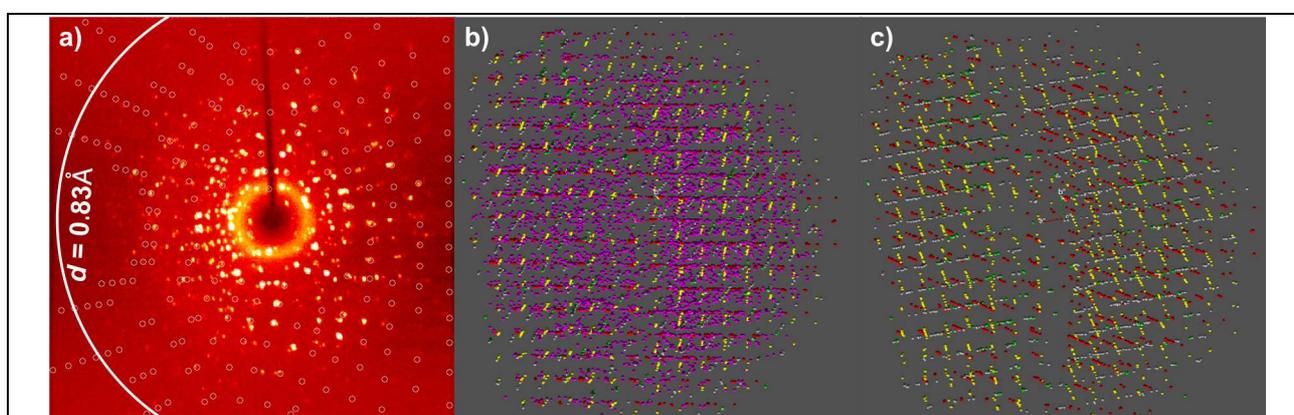


**Fig. 10** Raman spectra for pyrrolidine 6 hydrate at various temperatures.

### ***tert*-Butanol decahydrate [H2]**

The *tert*-butanol molecule can be considered as structural analogue of *tert*-butylamine. Both compounds contain the same aliphatic fragment. However, due to the different nature of the functional groups their properties will be different, like the melting points of the crystals. The amine, which was presented earlier, can form up to seven hydrates. In case of *tert*-butanol two crystalline hydrates containing 2 and 7 molecules of water per organic molecule are known [12].

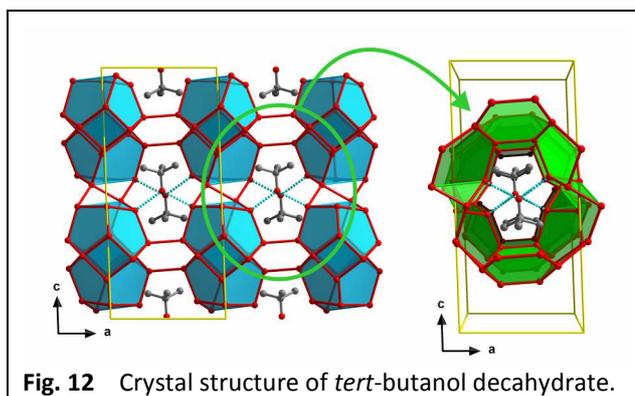
The structures of two polymorphs of the neat alcohol are described as well [67, 68]. In both hydrates, water molecules are organized in layers where alcohol-water hydrogen bonds occur. In the heptahydrate, these layers are additionally bonded together by the hydroxyl groups of the alcohol molecules located between them. While the *tert*-butylamine forms a whole series of hydrates, the question is whether similar properties are also inherent for the corresponding alcohol. *In situ* crystallization for a higher water content (molar ratio of alcohol: H<sub>2</sub>O equal to 1:10) gave a single crystal of *I<sub>h</sub>* ice polymorph. During a long process lasting many hours, the substance was simply separated and "purified" from organic impurities in the same way as during the zone melting process. Of course, the longer the crystallization process (slow movement of the IR laser beam along the capillary), the better the crystals can be obtained. Indeed, in the given case, this type of approach gave a hydrate of **group IV** in the form of a single crystal. However, I searched for a not-so-trivial and well-known structure. During further attempts to crystallize other *tert*-butanol hydrates, I decided to perform the entire process very quickly. The IR laser beam moved along a 0.4 mm diameter capillary at a speed of approx. 5 mm/min (from bottom to top) and the crystallization lasted about 2 minutes. The best quality of crystals can be expected slightly before the end of the position reached by the melting zone. Here the crystals should be of good shape and lack impurities and other differently oriented specimens. In the case of such a short measurement, however, the expectation of good quality crystals is far-reaching optimism. Indeed, the diffraction pattern recorded for the obtained phase was poor, similar to the distribution of the reflections in the reciprocal lattice as shown in **Figure 11**. However, a few (maybe a dozen or so) of networks with comparable unit cell parameters could be selected from the real jungle of the spots. They corresponded to the crystalline phase of a new, unknown *tert*-butanol hydrate. The rapid crystallization carried out resulted in the formation of an oligocrystalline phase composed of many components with slightly different orientations, which most probably grew in the form of bundles of needles. For such crystals, the problem with the overlap of reflections of all the networks will have an impact on the final discrepancy parameter during the structure refinement. The obtained structure corresponded to decahydrate and the *R*1 factor was slightly above 8% for the sample recorded at *T* = 100 K. At this temperature, only the hydrogen atoms were disordered in the same manner as observed in ice polymorphs *I<sub>h</sub>* or *I<sub>c</sub>*. Water molecules formed a three-dimensional network while the alcohol molecules were located in the channels and interacted



**Fig. 11.** Diffraction pattern for oligocrystalline sample of *tert*-butanol decahydrate **a)**, reflections in the reciprocal lattice **b), c)**.

with the H<sub>2</sub>O species *via* strong O-H...O hydrogen bonds. In the structure there were also irregular and deformed small cages, which can be treated as the 4<sup>3</sup>5<sup>6</sup> type. The structure of the alcohol decahydrate is shown in **Figure 12**.

At a higher temperature, the thermal ellipsoids of the atoms in the alcohol moiety are elongated which may suggest the disorder of this molecule. Although this decahydrate

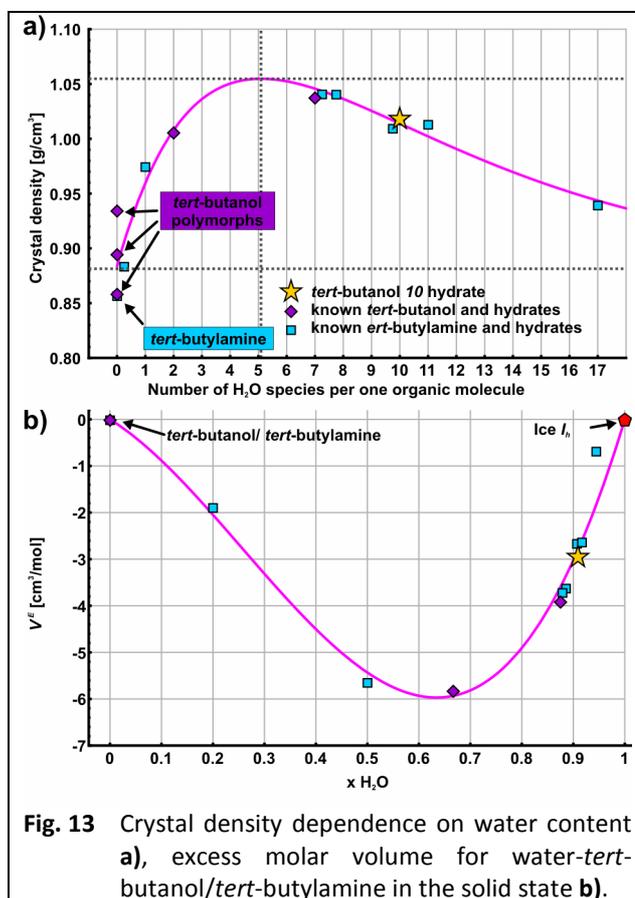


**Fig. 12** Crystal structure of *tert*-butanol decahydrate.

contains more water molecules than the 9¾ hydrate of *tert*-butylamine, it has a different character with the alcohol molecules incorporated in the network of water species. For *tert*-butylamine, such systems are formed with lower H<sub>2</sub>O content. In the case of 9¾ or 11 hydrate hydrates, however, very disordered structures resembling clathrate-hydrates are observed. For a series of hydrates of *tert*-butylamine and *tert*-butanol, an informative analysis of the dependence of their densities on the water content can be carried out, as well as an analysis of the excess molar volume. These relationships are presented in **Figure 13 a)** and **b)** respectively. Hydrates of both compounds can be treated as different hydration stages "frozen in a solid state" en route to the ice structure, *i.e.* a system with infinitely large dilution. In the case of the dependence of the density of crystals on the number of molecules of water (including the pure amine and alcohol phases), a four-parameter modified Morse potential function can be fitted

$$f(x) = s - d_e \cdot \left(1 - e^{(-a \cdot (x - r_e))}\right)^2$$

with the following parameters:  $s = 1.055$ ,  $d_e = 0.173$ ,  $a = 0.135$ ,  $r_e = 5.09$ . The  $s - d_e$  value corresponds to the density of a system containing only water (number of water molecules  $\rightarrow \infty$ ) and yields  $0.88 \text{ g/cm}^3$ . The actual density of the ice polymorph  $I_h$  at atmospheric pressure and  $T = 173 \text{ K}$  is equal to  $0.93 \text{ g/cm}^3$ . For the observed dependence, a gap can be seen where hydrates do not appear although their expected density and efficiency of packing should be the largest. As the content of water molecules increases, the molecular architecture of hydrates changes. For small H<sub>2</sub>O content the molecules are isolated; in the case of further hydration, these moieties organize in columns or layers. The last step is to surround the hydrated molecules and create a three-dimensional network of water molecules. However, for the encapsulation more molecules

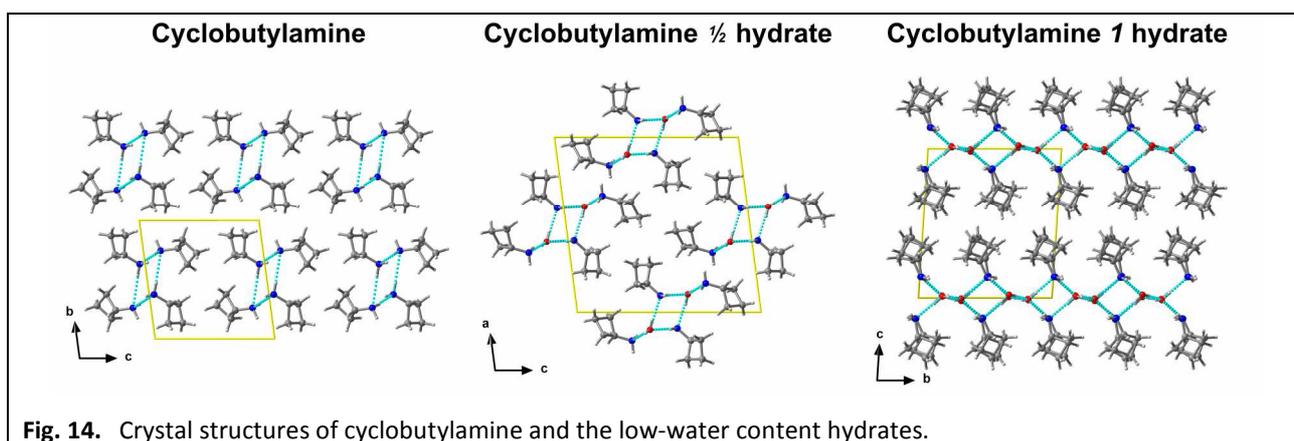


**Fig. 13** Crystal density dependence on water content **a)**, excess molar volume for water-*tert*-butanol/*tert*-butylamine in the solid state **b)**.

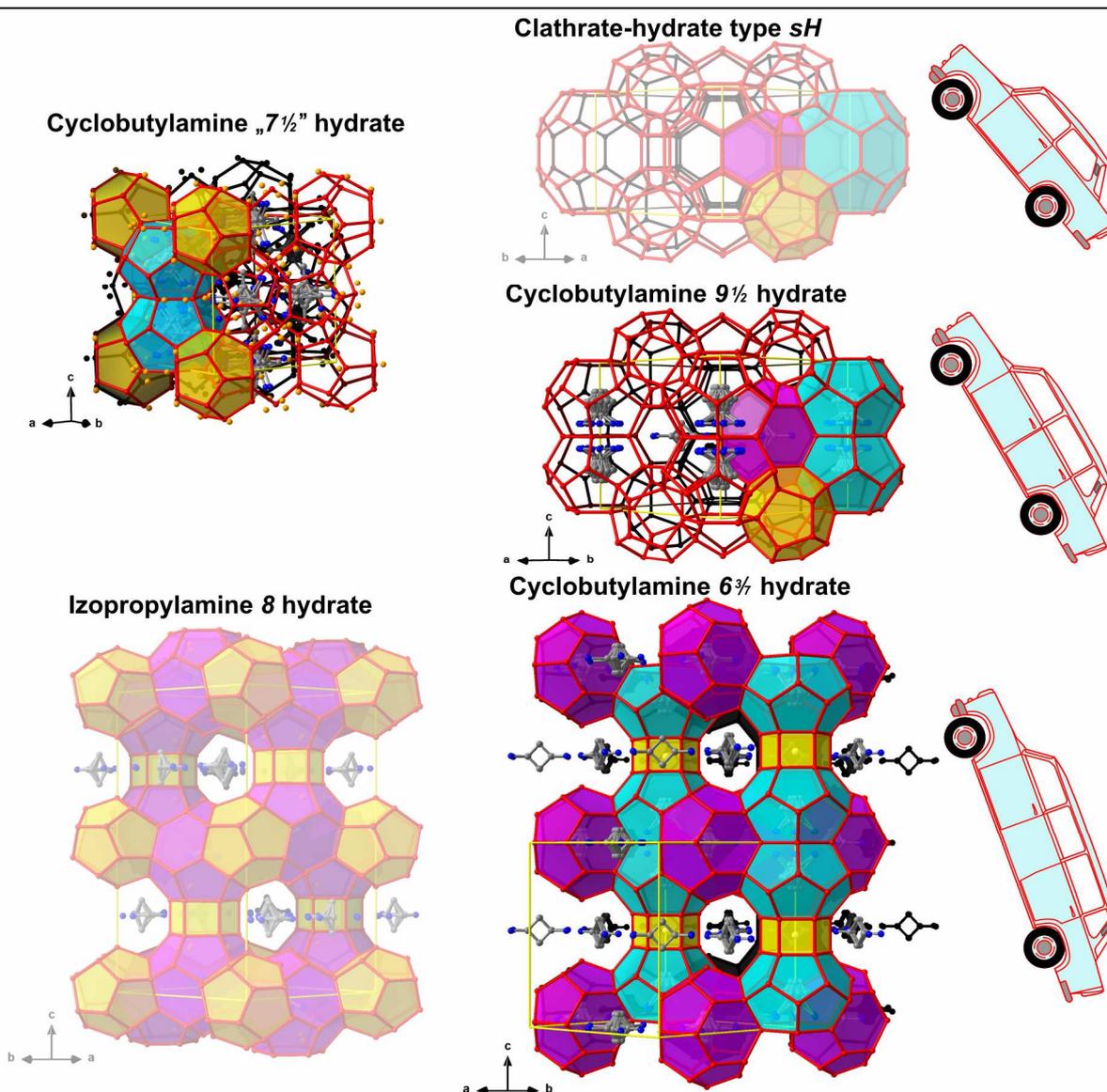
are needed, which creates the impression of a gap among the observed hydrates. A further increase in the water content results in the formation of smaller, empty cages in the structure giving crystals of yet lower density. Interestingly, the most thermally stable hydrates amongst those presented here are the ones with the highest water content. The dependence of the excess molar volume generated for the *tert*-butylamine and *tert*-butanol hydrates shows that these systems resemble the behavior of liquid mixtures where there is contraction as is the case, for example, in the water ethanol-system.

### Cyclobutylamine and hydrates [H4]

Cyclobutylamine is a primary amine with a four-membered aliphatic ring and a slightly less crowded amine group environment than in *tert*-butylamine. In the crystal structure of the neat amine there are two crystallographically independent molecules. They are joined in ribbons *via* N-H...N hydrogen bonds. In the case of one molecule, both hydrogen atoms of the amino group are engaged in this type of intermolecular interaction. In the second molecule, one of the hydrogen atoms of the -NH<sub>2</sub> fragment does not participate in such bond. The amine crystals melt at a relatively low temperature of 205 K, which is similar to *tert*-butylamine. In the case of cyclobutylamine, the structure of the hydrate containing 0.5 molecules of water per amine moiety is known [69]. However, this compound forms more hydrates. For a mixture with a molar ratio of 1:1, a monohydrate can be obtained. The structure is fully ordered at lower  $T = 100$  K and even at  $T = 202$  K, which is close to the melting point where higher vibrations of atoms and disorder can be expected. The hydrate contains layers of zigzag-shaped chains of water molecules and amino groups all interacting *via* hydrogen bonds. Aliphatic fragments are located on both sides of the layers. The structures of the amine and  $\frac{1}{2}$  and  $1$  hydrates are shown in **Figure 14**. In these systems, the amine and/or water molecules form well-defined hydrogen bonds. Although the monohydrate structure is ordered and well-defined, the final  $R1$  factor is just above 6%. This is affected by the quality of the crystals, which form a mixture of differently oriented crystallites. This requires integration of the data and refinement of the structure based on many partially overlapping lattices. With a higher water content, a three-dimensional H<sub>2</sub>O network is observed in the obtained hydrates. From a mixture of water:amine in a molar ratio of 1:2, two different cyclobutylamine hydrates were grown in two independent crystallization experiments. One of them is the trigonal  $6\frac{2}{3}$  hydrate; the other is " $7\frac{1}{2}$ " hydrate crystallizing in the cubic system. The structure of the hydrate with the lower water content can be solved and refined in two space



groups  $P\bar{3}m1$  and  $P6/mmm$ , which of course is not unusual in the universe of crystalline structures. Usually, if possible, the structure should be refined in the group of the highest possible symmetry. However, in the case of the cyclobutylamine discussed above, the refinement parameters for the hexagonal system both for higher (210 K) and lower temperature (100 K) are more than one percent higher which suggests that the correct symmetry is trigonal. In the  $6\frac{3}{2}$  hydrate, a network of two-dimensional channels is observed in which disordered amine molecules are located, forming rather weak hydrogen bonds with water molecules. In addition, in the crystal there are three types of cages:  $4^66^2$ ,  $5^{12}6^2$  and  $5^{12}6^3$ . The first one, which is too small is empty, while the remaining ones are occupied by disordered amine molecules where weak N...O interactions are also observed. The structure of this hydrate is similar to isopropylamine hydrate [40, 70], which also contains two-dimensional channels occupied by the organic molecule. The relative arrangement of channels, the types of cages and their distribution, and stoichiometry of the hydrate are however different in both cases. The next structure containing water and cyclobutylamine is a cubic " $7\frac{1}{2}$ " hydrate corresponding to the *sl* clathrate-hydrate. The entry in quotation marks means that it is not a stoichiometric system - the actual composition corresponds to a **7.543** hydrate. The disordered amine molecules occupy larger  $5^{12}6^2$  cages and the smaller  $5^{12}$  voids are empty. In addition, the network of water molecules is disordered where oxygen atoms occupy alternating positions (in relation to the 'ideal' structure) with occupancies not exceeding 8%. The non-stoichiometric composition of the hydrate results from replacing some of the water molecules with amine groups. The composition of the archetypal *sl* clathrate-hydrate with only the  $5^{12}6^2$  cages filled would correspond to the  $7\frac{3}{2}$  hydrate. From the literature data, based on the parameters of the unit cell and the symmetry of the crystal system, it is known that the hydrates corresponding to the *sl*-type systems also form with ethylamine or dimethylamine [40]. In this case, however, there is no structural data and therefore no basis for determining whether the structures are ordered or not. The obtained cyclobutylamine " $7\frac{1}{2}$ " hydrate is an example of a system with a disordered network of oxygen atoms of the H<sub>2</sub>O moieties, similar to the case of  $9\frac{3}{4}$ , **11** and **17** *tert*-butylamine hydrates. The next structure containing water and cyclobutylamine is a  $9\frac{1}{2}$  hydrate. It crystallizes from an 8:1 mixture of H<sub>2</sub>O:amine. As in the case of  $6\frac{3}{2}$  hydrate, the crystal structure can be refined in alternative space groups  $P\bar{3}1m$  and  $P6/mmm$ ; however, comparing discrepancy factors suggest that the hydrate belongs to the hexagonal system. This is a hydrate similar to clathrate-hydrate of the *sH* type. However, it contains additional water molecules located on the plane (002) passing through the centre of the unit cell. Such systems are known for trimethylamine [71]. The structures of the obtained higher cyclobutylamine hydrates and their comparison with known structures of the *sH* clathrate-hydrate and the isopropylamine octahydrate are shown in **Figure 15**. The structure of  $9\frac{1}{2}$  hydrate contains  $5^{12}$ ,  $5^{12}6^2$  and  $5^{12}6^3$  cages, of which the last two are occupied by the disordered amine molecules. The oxygen atoms of the water molecules, unlike the hydrogen atoms, are ordered.  $5^{12}6^2$  cages have hexagonal-shaped faces in common. The oxygen atoms forming the corners of these hexagons have considerably extended temperature factors, suggesting their disorder. There are weak hydrogen bonds between these atoms and disordered amine molecules. The  $6\frac{3}{2}$  and  $9\frac{1}{2}$  hydrate structures of cyclobutylamine represent the following stages of the *sH* clathrate-hydrate structure expansion



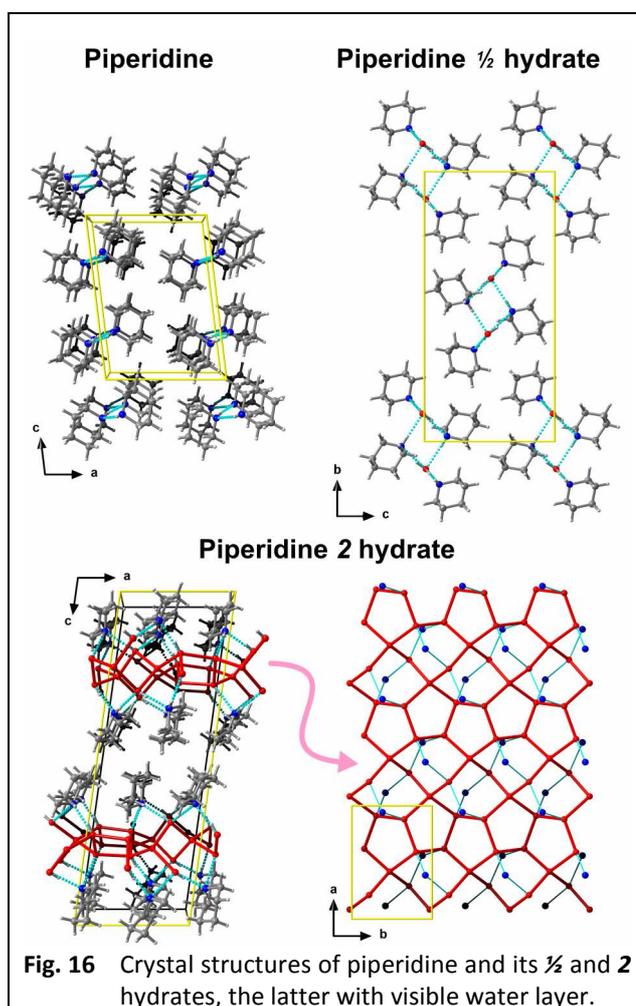
**Fig. 15** Crystal structures of water-rich cyclobutylamine hydrates compared with structures of isopropylamine **8** hydrate [70] and clathrate-hydrate type *sH*.

along the [001] axis, which can be compared to the construction of a limousine from an economy car (this analogy was used in the graphical abstract of the paper). The analysis of powder diffractograms collected for flash-cooled mixtures containing water and cyclobutylamine in molar ratios from 1:0.5 to 1:8 showed that, in this concentration range, all of the systems obtained by the *in situ* crystallization technique are formed with exception of to the "7½" hydrate. Some of the phases may coexist. Among the obtained crystals containing cyclobutylamine and water, the most stable is 9½ hydrate melting at 278 K. A slightly lower stability is demonstrated by the 6¾ hydrate (mp = 273 K). For a cubic "7½" hydrate, determination of the melting point was not possible - during the crystallization no pure phase was formed. Cyclobutylamine hydrates containing fewer water molecules (hemi- and monohydrate) melt at much lower temperatures.

### Piperidine and hydrates [H1]

The piperidine can be regarded as a structural analogue of pyrrolidine with a larger heterocyclic ring. The structure of the neat amine was already known [72]. Despite the similarity of both

amines and their comparable packing in piperidine crystals, it was not possible to observe the presence of another crystalline phase even near the melting point of the crystal (261 K). After dissolving the liquid amine in water, the solution warms up quite significantly, similarly as in the case of other amines described here. This means that the organic molecules are highly hydrated and hydrate formation may be also expected in the case of piperidine. Indeed, this compound forms a series of such systems, although they are not as numerous as the *tert*-butylamine case. The system with the lowest water content is the hemihydrate. It is a fully ordered structure. The amine and water molecules interacting through O-H...N and N-H...O hydrogen bonds form columns arranged along the direction [100]. The topology of hydrogen bonding is different in this case as compared with the pyrrolidine hemihydrate, where the interacting molecules form layers. The next crystal of piperidine with water is the dihydrate. In this case, the amine molecules are fully ordered and the position of the hydrogen atom of the NH group, similarly as in the case of the  $\frac{1}{2}$  hydrate, is equatorial. The water molecules are arranged in layers to which amine molecules are attached on both sides due to N-H...O contacts. The hydrogen atoms of water molecules exhibit disorder, but the positions of protons for N-H...O interactions are precisely defined. As for well-defined, ordered hydrates structures with low water content (pyrrolidine **6** hydrate, cyclobutylamine **1** hydrate and piperidine  $\frac{1}{2}$  hydrate) the O-H...N hydrogen bonds in piperidine dihydrate are clearly shorter than the N-H...O contacts. The topology of layers of water molecules in this dihydrate is rather unique among the structures of known hydrates of **group III** of organic compounds deposited in the CSD database. The structures of the neat amine,  $\frac{1}{2}$  and **2** hydrates are shown in **Figure 16**. Another system containing water is the **8.1** hydrate and the crystals, despite a slightly different composition, are isostructural with **8** isopropylamine hydrate [40, 70] whose structure is shown in **Figure 15**. A slightly different, non-stoichiometric composition of the piperidine hydrate results from the positioning of amine molecules together with bridging water molecules (having small occupancies) in two-dimensional channels. Additional piperidine molecules occupy larger  $5^{12}6^4$  cages; the remaining  $5^{12}$  and  $4^66^2$  remain vacant. In the solid state, the amines are so disordered that it was not possible to determine the positions of amino groups although, based on the proximity of the organic molecules, the presence of hydrogen bonds between amine and water can be deduced. Moreover, some of the oxygen atoms of the three-dimensional water molecule framework are also disordered.



In order of increasing number of water molecules per amine, the next system is the  $9\frac{3}{4}$  piperidine hydrate. This is a similar structure to the  $9\frac{3}{4}$  *tert*-butylamine hydrate in terms of both symmetry and disorder of the position of oxygen atoms in water molecules. The hydrogen atoms are disordered as well. Small cages remain vacant whereas, in large cages of the  $4^3 5^9 6^2 7^3$  type, amine molecules are located which are disordered to such an extent that it is not possible to determine the positions of amino groups. The volume of the unit cell of  $9\frac{3}{4}$  piperidine hydrate is bigger than in the case of *tert*-butylamine, which is undoubtedly affected by the less compact structure of the secondary amine. During the lowering of the temperature in the piperidine hydrate, there was lowering of symmetry probably connected with multiple twinning and partial cracking of the crystals. Very unfortunately for such a low-temperature phase, it was not even possible to solve the structure. The last hydrate observed for piperidine is the **11** hydrate, whose structure also corresponds to the *tert*-butylamine hydrate. The disordered amine molecule (with indistinguishable NH groups) occupies large cages  $4^{15} 5^{10} 6^6$  whereas small ones remain empty. Also in this case, the volume of the unit cell of the hydrate with the secondary amine is greater than the analogue containing *tert*-butylamine. Due to the structural similarities of the higher piperidine hydrates and the corresponding hydrates of isopropylamine and *tert*-butylamine, these structures have not been presented in a separate figure. The crystals of the **11** hydrate of piperidine are not stable and during the diffraction experiment they were slowly disintegrating into a powder form. Even lowering the temperature did not help; perversely, it even seemed to accelerate the process. Despite this, it was possible to collect reflections fast enough to obtain a valid structure refinement. Piperidine forms two hydrates with a high water content corresponding to *tert*-butylamine analogues. However, the primary amine can additionally crystallize in the form of a **17** hydrate. Approaches with rapid crystallization of piperidine mixtures with water for a wide range of molar ratios, from small water contents to 1:17 showed that, even from very diluted solutions, at most an **11** hydrate crystallizes. For this amine, no structure analogous to an *sII* clathrate-hydrate could be observed. For most piperidine hydrates (with the exception of the unstable phases of **11** hydrate), Raman spectra

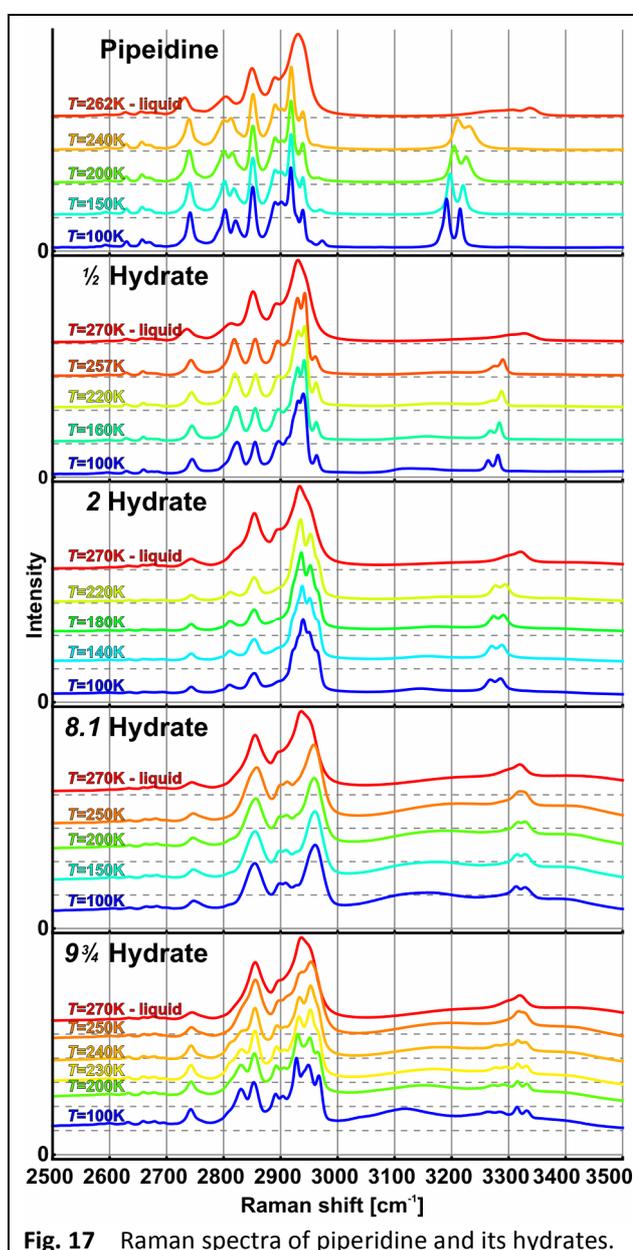


Fig. 17 Raman spectra of piperidine and its hydrates.

were recorded, both for solid phases at different temperatures and for solutions obtained after melting. These spectra in the frequency range corresponding to the stretching vibrations CH, OH and NH are shown in **Figure 17**. For the neat amine, the NH vibrational bands are located around  $3200\text{ cm}^{-1}$ . A double signal suggesting the dynamics of the NH group may be surprising. However, the structure of the amine is fully ordered. The presence of the doublet results from the coupling of hydrogen-bonded oscillators, which although symmetrically equivalent from a crystallographic point of view, are spectroscopically distinguishable and do not necessarily have to vibrate in the same phase. This phenomenon is known as Davydov splitting [73]. For the hemihydrate or dihydrate, the NH vibrational bands appear at ca  $3300\text{ cm}^{-1}$ . This position of the bands is related to the formation of N-H...O hydrogen bonds. The presence of the doublet results from the two crystallographically independent molecules of amines having slightly different molecular environments. For higher hydrates, where the amine molecules are surrounded by a water molecule framework and are involved in hydrogen bonds, the NH vibrational bands are clearly shifted above  $3300\text{ cm}^{-1}$ . This proves the presence of weaker N-H...O hydrogen bonds. Such systems more closely resemble clathrate-hydrates than the systems with well-defined and strong intermolecular interactions that exist in lower hydrates of amines. The spectra of crystalline **8.1** and **9.3** hydrates are similar to the spectra of solutions. The highest melting points are observed for the higher piperidine hydrates, although they do not exceed 270 K. The least stable is the hemihydrate melting at 249 K.

A kind of summary of hydrates of **groups III** or **V** of small organic compounds was given in the introduction of the **H1** paper where known crystal structures of compounds believed to have an impact on the structure of water in solutions were analysed. This structure-making or breaking effect can be extremely important in the case of proteins, which contain a hydration sphere and can be easily affected by the change of the structure of the surrounding water molecules. At the end of the 19th century, the influence of salt on the 'salting out' or dissolution of proteins in aqueous solutions was studied by Hofmeister [74]. Various anions and cations are now ranked into the Hofmeister series, otherwise known as the lyotropic series. This series takes into account the stabilizing and destabilizing properties of the ions on the quaternary structures of proteins. A popular compound used to salt-out proteins, while stabilizing their structures, is ammonium sulphate. In the case of salts, all ions will have an effect on the properties of the solution and these effects may oppose each other. These effects depend on many factors: in a simplified way, substances stabilizing the structures of proteins are called kosmotrops (*Greek*: κόσμος + τρόπος = order + making), while those that contribute to their denaturation are chaotropes (*Greek*: χάος + τρόπος = disorder + making) [75-77]. Electrically neutral molecules, especially those that are highly soluble in water, may be kosmotropes or chaotropes. The first group includes, for example, glucose, *tert*-butanol, glycine and proline; whereas the known chaotropes include, for example, methanol, ethanol, urea and THF. Sometimes the character of the compound may also depend on its concentration. In the case of the compounds mentioned above, no crystalline hydrates containing more water molecules were previously known (with the exception of *tert*-butanol heptahydrate). Known mono or dihydrates do not reflect the full nature of hydrated compounds -

too few water molecules result in the formation of ordered systems with well-defined hydrogen bonds. Only at higher dilution the hydrated molecules can show their real influence on the structure of the surrounding water molecules. Indeed, in the THF hydrate, a clathrate-hydrate structure is formed. On the other hand, in the case of pyrrolidine, which can be treated as a decarboxylated analogue of proline - a very strong kosmotrope, in the hexahydrate amine molecules are incorporated in the framework of water molecules, thus stabilizing their structure. Similar properties are seen for *tert*-butanol where, in the higher hydrates, the alcohol molecules form strong hydrogen bonds even for large dilutions, as in the decahydrate.

In the hydrates of other amines such as piperidine and cyclobutylamine presented in this work, there are interactions with H<sub>2</sub>O moieties (especially in hydrates with more water content) but they are relatively weak and the structures resemble clathrates-hydrates. In contrast, for *tert*-butylamine water systems with an intermediate water content of **7¼** and **7¾**, the hydrates are similar to structures typical for kosmotropes while ones richer in water content (*e.g.* **9¾**, **11** and **17** hydrates) resemble typical clathrate-hydrate chaotropes. As can be seen, not only the right size of the molecule, but also the appropriate functional groups are necessary to stabilize the water structure. The slightly larger fragment of the heterocyclic ring in the piperidine induces the formation of chaotrope-like hydrates. Substituting the amino group with hydroxyl in *tert*-butylamine yields a compound with kosmotropic properties. Pyrrolidine seems to have the ideal size for making the water structure ordered. While the amino group forms strong hydrogen bonds by forcing the directional proton system of H<sub>2</sub>O molecules, the hydrophobic fragment occupies a niche in a three-dimensional network of water molecules. Due to the basic nature of its amino group, neat pyrrolidine may of course be too reactive for macromolecules as opposed to proline. For the latter amino acid, additional interactions with the carboxyl group should be expected in aqueous solutions. In the case of ionic clathrate-hydrates, organic moieties such as hydrophobic tetramethylammonium or tetrabutylammonium cations having chaotropic properties will be located in cages, while hydrophilic F<sup>-</sup>, OH<sup>-</sup> or Cl<sup>-</sup> anions will incorporate in a three-dimensional network. In such systems there will be no hydrogen bonds between host and guest molecules.

## Summary

The presented collection of scientific papers is dedicated to structural studies of crystals, mainly hydrates, with different degrees of molecular disorder. The results were described in the context of an ideally ordered structure of two polymorphs containing DMANH<sup>+</sup> cations, chloride anions and H<sub>5</sub>O<sub>2</sub><sup>+</sup> moieties – *i.e.* a "hydrated proton" [**H8**]. For both forms, high-resolution X-ray diffraction measurements followed by multipole refinements were successfully performed. The ordering of protons in the structure was also confirmed by neutron diffraction measurements for one of the polymorphs. Although the structures of these crystals are fully ordered and stabilized by ionic interactions, these systems are relatively unstable and disintegrate when removed from the mother liquid.

The disorder can have a huge impact on the final quality of the refined structure, especially if is not properly modelled or is simply not taken into account. The example shown here was alizarin

[H7]. Applying a correct disorder model and including the twinning effect for both polymorphs of this dye - the known one and the new one presented in [H7] for the first time – allowed reliable crystal structures to be obtained. Oversight of the disorder affects not only the quality of the final structure but can also lead to inadequate conclusions about the composition of the crystal. When the disordered water molecule of relatively small occupancy is not included in the structure of 4,4'-bipiperidinium chloride **0.12** hydrate, apparently acceptable structural data are obtained; but in fact such a structure is incorrect [H3].

Accurate determination of the structure is important for the classification of various systems. In the case of structures with high water content, clathrate-hydrates may be formed where there will be no hydrogen bonds between H<sub>2</sub>O and guest molecules. Typical examples of such systems are methane clathrate-hydrates. In the case of amines, **9¾** *tert*-butylamine hydrate was considered to be a fully inclusive structure *i.e.* true clathrate-hydrate. This is rather unusual as amines tend to form N-H...O hydrogen bonds in structures of hydrates. Indeed, precise structural studies performed for *tert*-butylamine showed that, in fact, the structure of the **9¾** hydrate has such interactions; moreover the network of water molecules is disordered [H6]. This amine forms a whole series of hydrates (seven structures) being the most frequently hydrated neutral molecule of an organic compound. Although hydrates rich in water really resemble clathrate-hydrates, in all the observed structures there are "host"- "guest" interactions. The structures of *tert*-butylamine hydrates, along with such compounds formed by *tert*-butanol [H2], may be considered as 'frozen' (in the solid state) successive steps of hydration of increasingly diluted solutions en route to pure ice. In the case of THF, its **17** hydrate should be considered as the real clathrate-hydrate structure. Accurate structural studies have shown that a disordered molecule of this popular solvent occupies large cages formed in the 3-D framework of water molecules, having no directional interactions with water molecules [H5]. In addition, this system crystallizes relatively easily over a wide range of THF concentrations.

The structures of water-rich cyclobutylamine [H4] and piperidine [H1] hydrates, similar to *tert*-butylamine **9¾**, **11** or **17** hydrates, resemble clathrate-hydrates. However, due to the presence of "host"- "guest" interactions, they do not belong to this class of systems. In the hydrates of these compounds, the amine molecules occupying the cages or voids are largely disordered. The positions of the oxygen atoms of H<sub>2</sub>O molecules of the water frameworks are disordered as well. These amines both form five hydrates.

The structure of pyrrolidine hexahydrate [H5] looks different. The low-temperature polymorph is fully ordered, including the amine molecule as well as the positions of the oxygen and hydrogen atoms of H<sub>2</sub>O molecules. In this structure, the amino group is involved in strong hydrogen bonds with water molecules, while the aliphatic fragment is located in the niche present in the three-dimensional framework of H<sub>2</sub>O species. A similar structure is observed for *tert*-butanol decahydrate [H2], whose crystals were obtained extremely quickly (in tens of seconds), otherwise only hexagonal ice would be formed. The alcohol, embedded in a network of water molecules, forms well-defined hydrogen bonds with the solvent moieties.

With a low water content, all compounds described form very similar hemi-, mono-, *etc.* hydrates, usually with ordered structures and well-defined interactions with water. For higher hydrate

formation (hexa, heptahydrates, etc.) more water species are needed for partial or total enclathration/encapsulation of the hydrated molecules in a three-dimensional water network. It is only with this larger number of H<sub>2</sub>O molecules that the hydrated molecules exhibit their organizing (structure making) or disorganizing (structure breaking) influence on the structure of surrounding water. The formation of clathrate-hydrates (or similar systems with a strong disorder of guest molecules and H<sub>2</sub>O networks) is typical for chaotropes. Those hydrates where organic compounds are incorporated into the network of H<sub>2</sub>O *via* strong hydrogen bonds are typical for kosmotropes [H1]. Among the systems presented here, chaotropes include THF, high dilutions of *tert*-butylamine, cyclobutylamine or piperidine. The kosmotropes are pyrrolidine and *tert*-butanol. Despite the arrangement of the structures and the relatively high density of crystals containing low amounts of water, these systems are characterized by lower thermal stabilities than structures richer in water, which are more disordered and therefore show higher entropy.

Investigations of compounds and their mixtures with water, which at atmospheric pressure and room temperature are very volatile liquids (*tert*-butylamine, THF, pyrrolidine, cyclobutylamine, piperidine) or easily melting crystals (*tert*-butanol) would not be possible without the use of an *in situ* crystallization technique such as the zone melting method. The investigated liquid sealed in a capillary is mounted on the goniometer of a single crystal diffractometer where the sample can easily be solidified using a low temperature device. The crystallization is performed with the help of an IR laser beam focused on the capillary. Installations of this type uncommon. In Poland, such equipment exists only in the prof. Jan Czochralski Advanced Crystal Engineering Laboratory at the Faculty of Chemistry of the University of Warsaw. Together with prof. Michał K. Cyrański, I had the pleasure to co-create this laboratory. Regarding the *in situ* crystallization equipment, I performed all the necessary installations needed to couple the IR laser with the Bruker D8 Venture single crystal diffractometer. It was then the first such installation in the world on this machine.

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## 5. Summary of scientific achievements

- Published papers: **73** (all listed by ISI, including 53 papers published with PhD degree)\*
  - Hirsch index: **13**
  - Sum of times cited: **573** (535 without self citations)
  - Overall *IF*: **224**
- **46** conference presentations (lectures, oral presentations, posters)
- **11** promoted MSc students (8 as supervisor, 3 as co-supervisor)
- Long-term scientific stays:
  - 15-months postdoctoral fellowship with prof. R. Boese, University of Duisburg-Essen, Essen, Germany within KOLUMB Stipend granted by Foundation for Polish Science (**VIII 2009 – X 2010**)
  - 3-months postdoctoral fellowship with prof. M. K. Cyrański, University of Warsaw (**XII 2010 – II 2011**)
- Principal Investigator function in scientific grants:
  - Iuventus Plus project „*Crystal engineering of novel inorganic-organic hybrid systems. Synthesis, structure, properties and applications.*” granted by Ministry of Polish Science (**I 2011 – XII 2011**)
  - Project „*Hydrates of alcohols and ethers – structure, stability and properties*” granted by Foundation for Polish Science based on the European Union Regional Development Fund (**VII 2012 – IX 2014**)
  - SONATA BIS 6 project „*Crystal Engineering of alcohols and amines*” granted by National Science Centre, Poland (**VII 2017 – VI 2022**)



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\*Based on Web of Science (WoS) search performed on 20.03.2019