Final report

on the OTKA Pd project 128504 entitled „Supramolecular interactions and polymorphy, effect of temperature and pressure" started in 2018.

The aim of the project was to investigate important new materials from various fields (e.g. catalysis, medicinal substances, energetics, etc.); to identify polymorphs, solvatomorphs and co-crystals, and to explore their structural properties and secondary interactions, using the Single-crystal X-Ray Diffraction (SXRD) method. Thiourea (**1.1.**) and borane (**1.2.**) organocatalysts were examined, which are more advantageous for environmental protection and sustainability than metal-containing catalysts. Organocatalysts crystallization with different substrates can contribute a better understanding of their mechanism of action. Drugs were examined (e.g.: nitrofurazone (**2.1.**), drotaverine (**2.2.**), donepezil, tiofanat) and metal-containing (Cu and Ru and Rh "half-sandwich") complexes (**2.3.**) (under development) to explore the relationship between structure and biological effect. The structure of aromatic - non-aromatic systems were also investigated (**3.1.**, **3.2.**, **3.3.**), it can be used in the field of energy storage and charge transfer, charge transfer, solar cell systems. The effect of different functional groups on chiral separations were also examined (**4.**): chiral organophosphorus compounds were separated using spiro-TADDOL. We found a new highly porous crystal-forming metal-free organic frameworks (not MOFs, iHOFs) (**5.**). Organic frameworks can be used in many fields, such as separation, storage, sensing, heterogeneous catalysis or drug delivery. Highly porous crystals were formed by different functional groups on the same frame.

Several single crystal X-ray diffraction (SXRD) method was used to study the structure, and several crystal structures were exposed by temperature and were grown at non-ambient conditions. Under this OTKA project more than 200 different crystal structure were grown and measured, and structure analysis were completed. From these, 32 new crystal structures have been deposited in the Cambridge Structural Database (CSD) and 28 are published in an article (in 2022 September). The results were published in 15 articles in peer-reviewed international journals. The scientific outcome is the result of several collaborations with researchers from the Research Centre for Natural Sciences (TTK), the Budapest University of Technology and Economics (BUTE) and University of Szeged (SU).

Due to unforeseen economic difficulties and the COVID-19 epidemic, the introduction of the use of high pressure was moved later in time than we had planned in the application. But in the final year of the project, we were able to acquire all the parts for high pressure device (Diamond Anvil Cell, the necessary diamonds and a drilling machine), which crystallization in the cell can be carried out at high pressure, and the first experiments were carried out successfully. Collaborating with synthetic chemistry research groups and other research groups, a number of compounds were selected for testing under non-ambient conditions. These compounds were synthesised by Tibor Soós (TTK), Attila Domján (TTK), Gábor London (TTK), Ilona Kovács (BMGE) and Péter Bagi (BMGE). During the project, a lot of experiment have been performed.

During the project, 8 MSc students joined to the research and learned the theory and practice of the SXRD technique. I supervised 4 students, (more details on the end of the report). I was participated in the education in the University (in the subject general chemical laboratory practices; advanced lectures of inorganic chemistry; drug formulation laboratory practices; chemical calculation practices) and in the secondary summer school as well (Summer School for talented student). I led a program during the researchers' night program in 2019 as well. The IUCR conference was attend during the COVID pandemic in 2021 online and Conference of the Department of crystallisation and drug formulation, Association of Hungarian Chemist in 2022, Pécs.

High temperature investigation: The high temperature investigations are available in the Chemical Crystallography research group now. Differential Scanning Calorimeter machine (DSC) was used for the polymorphs investigation, solvent inclusion and melting point determination. The visible investigation was followed by hot stage thermal tool, and the classical chemical laboratory equipment.

High pressure investigation: We discussed our project with Professor Andrzej Katrusiak at Adam Mickiewicz University, Poznan, Poland and Univ.-Prof. Mag. Dr. Ronald Miletich-Pawliczek, Universitat Wien, Austria who are the expert in the field of high pressure investigation. The needed diamond anvil cell (DAC) for the high pressure investigation was purchased by a new company, Almax easyLab Ltd. who entered the market with smaller DAC cell a few years ago. The biggest problem for the use of the DAC cell was the production of the 0.2 mm diameter hole on a steel plate. We successfully solve this problem, and acquired a precision drill and a reinforced drill of the appropriate diameter for the use of the DAC cell. (The DAC cell and all other required tools were acquired within the framework of the related OTKA K 124544 of Petra Bombicz). Based on consultation with Rigaku's developers, it is not possible to use the DAC cell with our own Rigaku X-ray equipment, since, in addition to technical difficulties, the software evaluation cannot be solved with this old (2003) equipment. But within the framework of collaborations, we will be able to test the measurement in the DAC cell on newer types of diffractometers, which is included in our future plans.

1. Organocatalyst

1.1. Thiourea type of available organocatalysts were investigated under different conditions. Thiourea containing organocatalysts means the molecule contains a thiourea central part, works like an enzyme, and it is metal free. The chosen catalyst contains a isoquinoline, a quinoline and an electron withdrawing 3,5-bis(trifluoromethyl)phenyl-group. The catalysts were used as a well-recognized catalysts for the enantioselective synthesis like Michael addition.

The results of thiourea organocatalysts show similar synthon interactions (similar hydrogen-bond systems) between the donor thiourea and the acceptor base part of the compound. The water molecule was the smallest molecule which can be placed between them bridging as hydrogen bond donor and hydrogen acceptor species between the thiourea and isoquinoline. Polymorphs, solvent inclusion an cocrystals were also crystallised with water molecules (**Fig. 1.**) (the article is ready to submit). The larger substrate molecule crystallisations sometimes crystallises alone [Varga, Szilárd ; Angyal, Péter ; Martin, Gábor ; Egyed, Orsolya ; **Holczbauer, Tamás**; "Total Syntheses of (−)-Minovincine and (−)-Aspidofractinine through a Sequence of Cascade Reactions", Soós, Tibor ANGEWANDTE CHEMIE-INTERNATIONAL EDITION 59 : 32 pp. 13547-13551. Paper: anie.202004769 , 5 p. (2020)].

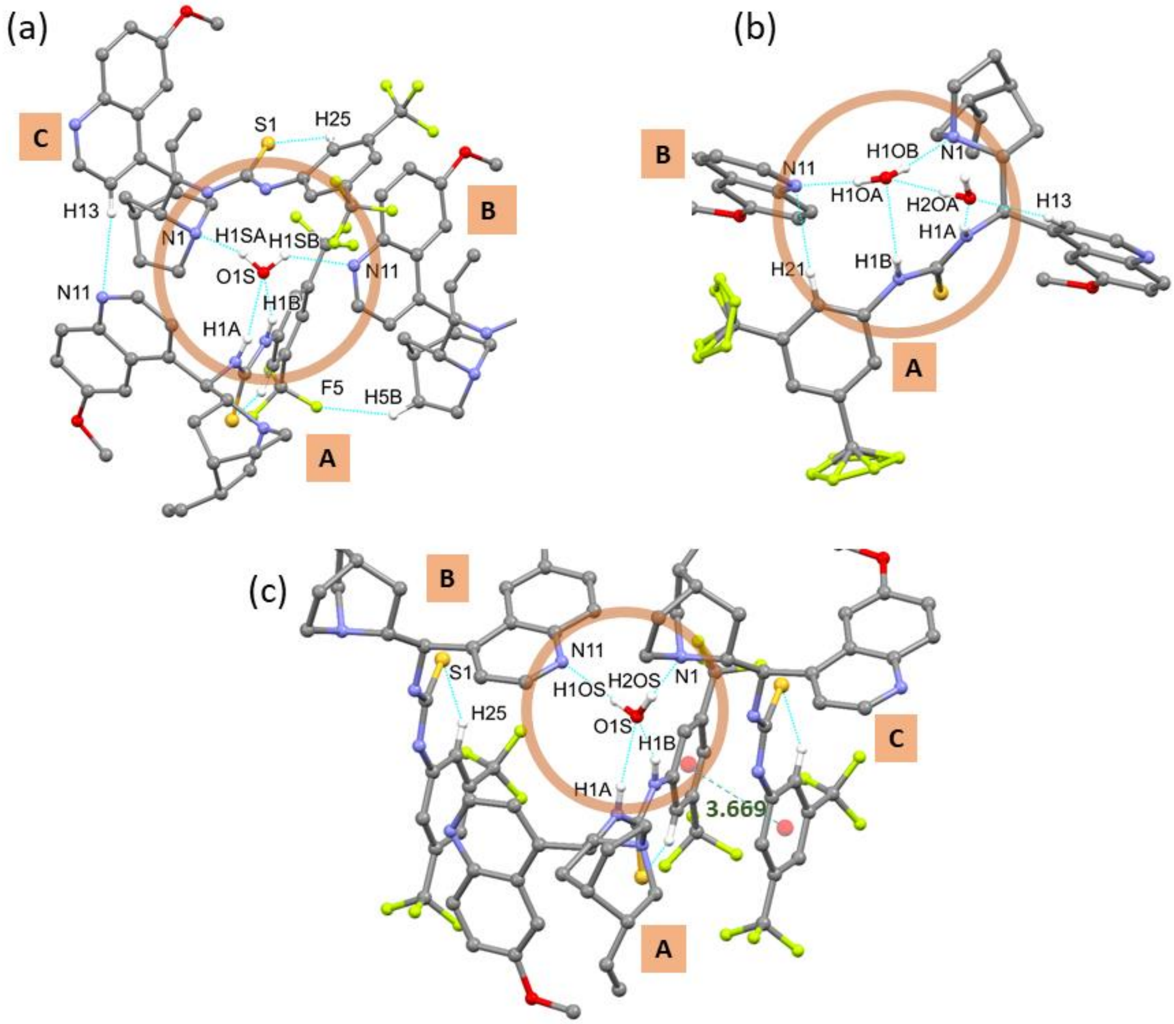

Fig. 1. The arrangement of the thiourea organocatalyst molecules around water molecule(s) in three different solvatomorph crystals

1.2. The catalytic hydrogenation by a nitrogen and boron containing (frustrated Lewis pair) molecules were described before. The distances of electron poor boron and electron rich nitrogen atoms can fine tuning with the space filling of these molecules. Electron distribution on the boron and on nitrogen atoms are also an important key. The electron distribution was fine-tuning by the substituent on the phenyl group. We investigated the same borane catalysts (10 kinds) with different primary, secondary or tertiary amines.

Different borane molecules were crystallised with nitrogen containing molecules (**Fig. 2.**). 18 new crystal structure was established and analysed. DSC and Hot stage investigation was completed, some DFT calculation was started (by Máté Berta (ELTE)). An MSc thesis has been written in this topic by Dávid Lovasi (patent was written, thesis was encrypted for four years).

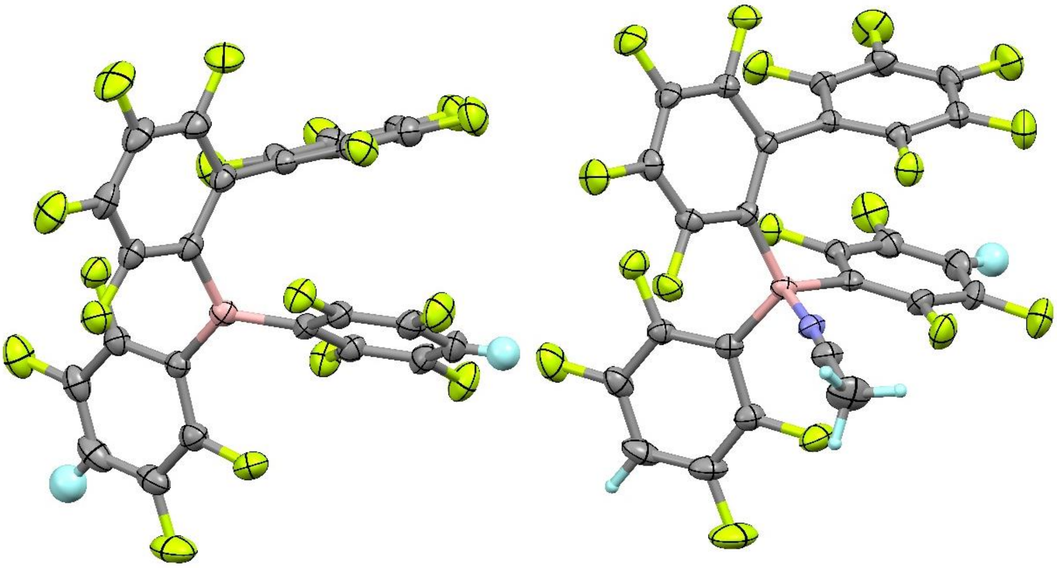

Fig. 2. The same borane with different conformation after an acetonitril is connected to the boron atom (righmolecule).

2. Investigation of Active Pharmaceutical Ingredients (APIs)

2.1. Polimorphy and co-crystal investigation of (E)-2-((5-nitrofuran-2-yl)methylene)hydrazine-1-carboxamide-nitrofurazone

The nitrofurazone is used for the treatment of bacterial skin infections, wounds, burns, and ulcers in the tropical area. The nitrofurazone compound has also been chosen as new API compound for investigations. 15 new polymorphs, cocrystals and solvent containing crystal structures were analised (**Fig. 3.**). Only two conformers was observed of the eight possible ones among the polymorphs, and another conformation can also be observed among the cocrystals. The stability of some crystals were investigated in different conditions: temperature, solvents and light.

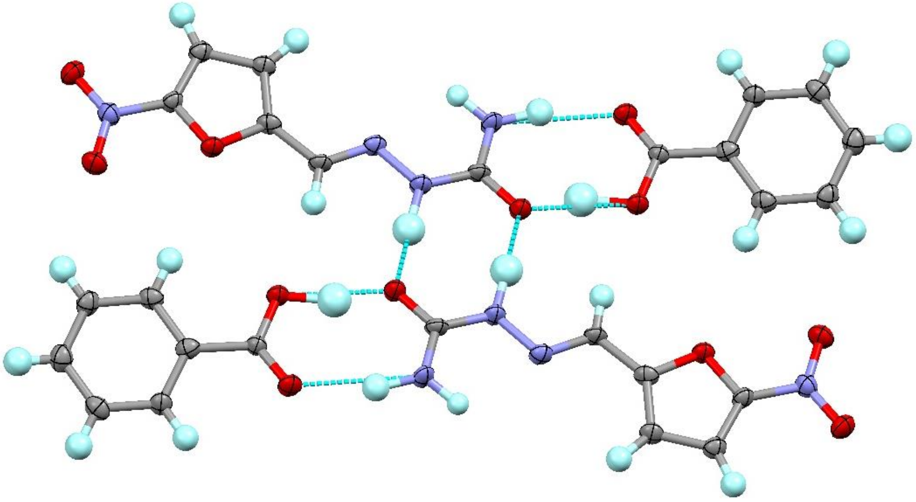

Fig. 3. The hydrogen-bond motifs of nitrofurazone and benzoic acid co-crystal

2.2. 1-(3,4-diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride drotaverin

Some drotaverine-like molecules was searched and compared in the Cambridge Structural Database (shortly CSD). In the literature, the free base compounds (i.e. 1-(3,4-Dimethoxyphenyl)methyl-6,7-dimethoxyisoquinoline (papaverine)) were found. The papaverine was crystallised with hydrochloride and alkyl-halogenide in most of the cases. The nitrogen atom of isoquinoline derivative rings were alkylated with different alkyl groups, and halogen anions were used as counter ions, i.e. methyl iodide. In the case of drotaverin and papaverine crystals, parallel π… π aromatic interactions were detected between the isoquinoline derivative rings. The planarity of isoquinoline rings are important to that type of π… π interactions. An other way of growing stable crystals is the crystallisation of the compound with transition metal halogenides.

We have co-crystallised some new drotaverine compounds with the homologue series of substituted acetic acids(**Fig. 4.**). The guest carboxylic acid molecules have been systematically examined in the crystal structures. Kitti Berecz (ELTE, BSc student) crystallised the missing carboxylic drotaverine host-guest system. Kitti Berecz wrote a BSc thesis from the results. (Kitti Berecz try to crystallise some other APIs (sertraline, donepezil, tiofanat) succesfully.)

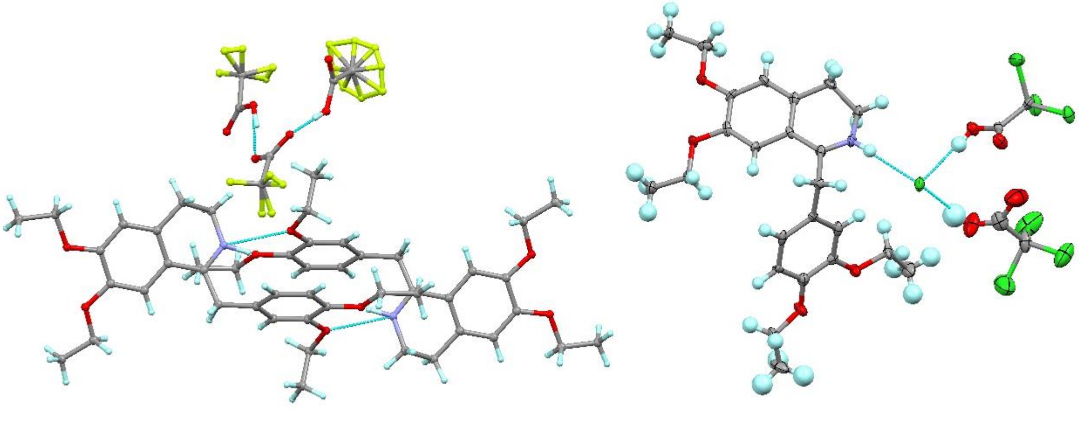

Fig. 4. Different hydrogen bond motifs are observable in the crystal lattices with trifluoroacetic acid (left) and trichloroacetic acid (right).

2.3. Structural investigation of possibly metallopharmaceutical candidates

In collaboration with Éva A. Enyedy and her research group in Department of Inorganic and Analytical Chemistry, Interdisciplinary Excellence Centre in the University of Szeged; transition metal complexes were investigated as possible bioactive chelator compounds. The results were published in three different journals in the recent years. All of the tested materials were new metallopharmaceutical candidates: thiosemicarbazone and hydroxypyridine-carboxylic acid derivatives with copper (II), and 2,2′-bipyridine or picolinate derivatives with rhodium(η5-C5Me5) and ruthenium(η6-toluene) “piano-stool” complexes and their single-ligands. The main objectives were to grow single-crystals of the free ligands and their complexes, determine their structures by SXRD measurement and evaluate their conformation and compare with other known structures. The final goal is to collect an appropriate amount of structural and biological activity data, which allows the investigation of structure-function relationships. Some complexes showed significant cytotoxicity in A2780 and MES-SA cancer cell lines and in the cisplatin-resistant A2780cis cells. The crystal structure of five Ru(Tol) and Rh(Cp*) complexes have been determined - with dimethyl-bipyridyl and dipicolinate ligands - and their expected piano-stool geometry was proven. In the received samples, an unexpected side product was found, which has a distorted octahedral molecular geometry. The presence of the side product both as in terms of the synthesis and the biological analysis can be useful feedback. An MSc thesis was written based on these results by Márk Dénes with my co-supervision. [1. Meszaros, JP; Pape, VFS; Szakacs, G; Nemeti, G; Denes, M; **Holczbauer, T**; May, NV; Enyedy, EA, DALTON TRANSACTIONS, 2021, 23, 8218-8231]; [2. Meszaros, JP; Nemeti, G; Poljarevic, JM; **Holczbauer, T**; May, NV; Enyedy, EA, EUROPEAN JOURNAL OF INORGANIC CHEMISTRY, 2021, 19, 1858-1868.]; [3. May, NV; Nys, K; Ching, HYV; Bereczki, L; **Holczbauer, T**; Di Marco, VB; Bombicz, P., ACTA CRYSTALLOGRAPHICA SECTION B-STRUCTURAL SCIENCE CRYSTAL ENGINEERING AND MATERIALS 2021,77, 193-204. [4.Petrasheuskaya, Tatsiana V ; Kiss, Márton A ; Dömötör, Orsolya ; **Holczbauer, Tamas** ; May, Nóra Veronika ; Spengler, Gabriella ; Kincses, Annamária ; Čipak Gašparović, Ana ; Frank, Eva ; Enyedy, Eva Anna NEW JOURNAL OF CHEMISTRY 2020, 44 pp. 12154—12168. (2020)].

3. Aromatic and antiaromatic compounds

These compounds may have interesting properties at high pressure (according to a presentation which was given by Miriam Pena-Álvarez in Poznan, Poland 2017 at High 55th European High Pressure Research Group Meeting; and her paper: G. E. Rudebusch, G. L. Espejo, J. L. Zafra, M. Peña-Alvarez, S. N. Spisak, K. Fukuda, Z. Wei, M. Nakano, M. A. Petrukhina, J. Casado, M. M. Haley J. Am. Chem. Soc., 2016, 138, 12648−12654.) According to the calculations of this group, high pressure is able to make irreversible $\pi \ldots \pi$ interaction between the aromatic rings.

3.1. 1-(4-methoxyphenyl)-2,3-diphenylpentaleno[1,2-a]biphenylene- aromatic

In cooperation with Dr. Gábor London and his Functional Organic Materials Research Group in the research Centre for Natural Sciences we investigated some new aromatic and antiaromatic compounds. We determined the structure of some single crystals at room pressure, to identify the network of supramolecular interactions. We were investigating charge transfer complexes and aromaticity and anti-aromaticity as well. The high accuracy of single-crystal X-ray diffraction measurements makes it possible to examine the degree of aromaticity in aromatic and non-aromatic systems based on bond lengths determined with high accuracy. Three crystal structures have been determined and one article has been published so far. [Mayer, Péter J. ; El Bakouri, Ouissam ; **Holczbauer, Tamás** ;

Samu, Gergely F. ; Janáky, Csaba ; Ottosson, Henrik; London, Gábor JOURNAL OF ORGANIC CHEMISTRY 85 pp. 5158-5172. , 15 p. (2020)].

3.2. Biphenylene, tetracyanoethylene (TCNE) and similar compounds

Dr. Gábor London proposed the synthesis and investigation of new aromatics and antiaromatics compounds and we involved Rita Dobszay (MSc student, ELTE) to crystallize these compounds (e.g.: pentalene, biphenyl with ethene-1,1,2,2-tetracarbonitrile) in the field of charge transfer complexes (**Fig. 5.**). She wrote her thesis in this topic. Collaborating with Dr Attila Domján (NMR Research Laboratory, TTK), we investigated biphenylene: TCNE as a possible charge-transfer complexes under high pressure. Tetracyanoquinodimethane and 1,2,4,5-tetracyanobenzene biphenylene were also investigated. We have some positive preliminary results at high pressure by NMR.

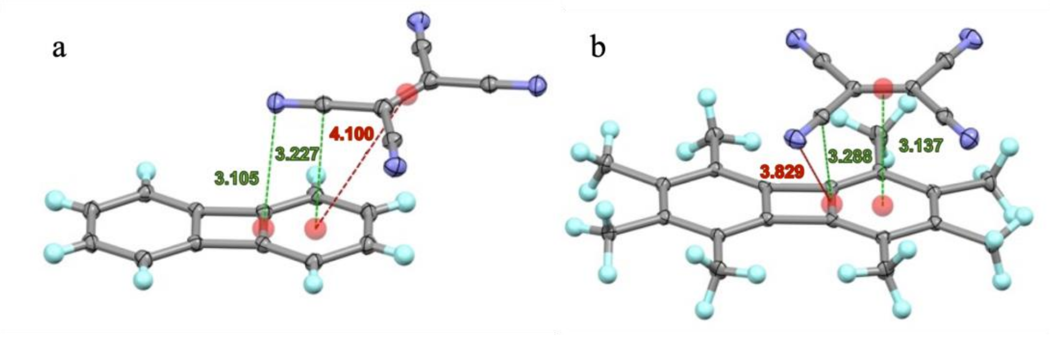

Fig. 5. The arrangement of the molecules in the asymmetric unit of TCNE-biphenylene (a) or TCNE-octamethylbiphenylene (b) co-crystals. The atomic distances between the TCNE and biphenylene or octamethylbiphenylene molecules are indicated.

An azabenzene unit containing Pd-complex was presented as a photo-switchable molecule. (Catalysis can modulate with different light wavelength.) The effect of substrate, catalyst concentration, light intensity was studied in a published study.

[Kunfi Attila, Jablonkai István, Gazdag Tamás, Mayer Péter J., Kalapos Péter Pál, Németh Krisztina, **Holczbauer Tamás**, London Gábor, RSC ADVANCES 11: (38) pp. 23419-23429., 2021 *]; [Gazdag Tamás, Mayer Péter J., Kalapos Péter Pál, **Holczbauer Tamás**, El Bakouri Ouissam, London Gábor, ACS OMEGA 7: (10) pp. 8336-8349., 2022 *];] [Áron Adorján, Péter J. Mayer, Pál T. Szabó, **Tamás Holczbauer**, Gábor London, Synthetic Communications (Early Access), 2022].

3.3. Aromaticity of 1,2-silole-2,5-diyl containing rings

(3,4-diphenyl-1l2-silole-2,5-diyl)bis(diisopropylphosphane) and derivatives were crystallised and four was published. The rotation of the phosphorous part is depending on the size of the substituents on the phosphorous atoms. [Mokrai, Réka ; **Holczbauer, Tamás** ; Fekete, Csaba ; Volk, Balázs ; Dorcet, Vincent ; Bouit, Pierre-Antione ; Nyulászi, László; Hissler, Muriel; Kovács, Ilona; Benkő, Zoltán EUROPEAN JOURNAL OF INORGANIC CHEMISTRY 2020: 18 pp. 1794-1802. , 27 p. (2020)] (**Fig. 6.**).

Diketonato-silole compounds were investigated in collaboration with Dr. Ilona Kovács and her research group in Department of Inorganic and Analytical Chemistry, BUTE. 5 new compounds were investigated and a dissertation was submitted to the Students' Scientific Conference (TDK) and an MSc thesis was written by Balázs Szatmári (BUTE/BME). The results will be published in the next year, after a few question would be answered.

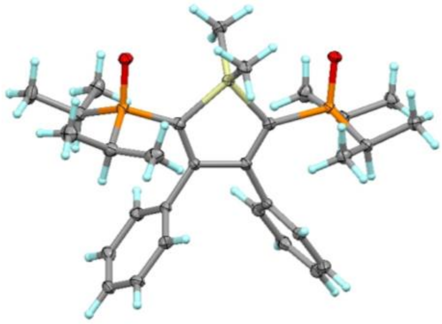

Fig. 6. Phosphanyl-substituted siloles and their P-modified congeners

4. Resolution of racemic compounds by crystallisation

4.1. Resolution of Dialkyl-Arylphosphine Oxides with TADDOL Derivatives

Dialkyl-arylphosphine oxide racemates were prepared and elaborated with guest TADDOL derivatives [Varga, Bence ; Herbay, Réka ; Székely, György ; **Holczbauer, Tamás** ; Madarász, János ; Mátravölgyi, Béla ; Fogassy, Elemér ; Keglevich, György ; Bagi, Peter EUROPEAN JOURNAL OF ORGANIC CHEMISTRY 2020: 12 pp. 1840-1852. 13 p. (2020)]. The chiral host-guest molecules were separated into two crystals. Single crystals were successfully grown from the diastereomers containing spiro-TADDOL [(R,R)-9] and (R)-methylphenylpropylphosphine oxide [(R)-2] or (S)-ethyl-phenylpropylphosphine oxide [(S)-3], allowing us to investigate the second order interactions: I calculated and analysed the Hirsfeld surface and DFT calculation as well, which helped us to identify the main secondary interactions in the crystal lattices.

(S)-(2-methylphenyl)-phenylphosphine oxide -((2R,3R)-1,4-dioxaspiro[4.5]decane-2,3-diyl)bis(diphenylmethanol) host molecule was prepared and elaborated with guest TADDOL derivatives. Similar phosphorus groups were used for the systematic supramolecular interaction investigation. Two similar molecules were crystallised and 5 other crystals were measured. The supramolecular interaction patterns were studied in similar structures by Hirshfeld and DFT calculation. Stability was also investigated in different conditions as well. The results were explained in detail in two articles. [Varga Bence, Szemesi Péter, Nagy Petra, Herbay Réka, **Holczbauer Tamás**, Fogassy Elemér, Keglevich György, Bagi Péter: Enantioseparation of P-Stereogenic Secondary Phosphine Oxides and Their Stereospecific Transformation to Various Tertiary Phosphine Oxides and a Thiophosphinate, JOURNAL OF ORGANIC CHEMISTRY 86: (21) pp. 14493-14507., 2021]; [Varga Bence, Vincze Daniella, Pető Hajnalka, Buna Levente, Pauló János, **Holczbauer Tamas**, Mátravölgyi Béla, Hegedűs László, Fogassy Elemér, Keglevich György, Bagi Péter: Resolution of aryl-H-phosphinates applied in the synthesis of P-stereogenic compounds including a Brønsted acid NMR solvating agent, ORGANIC CHEMISTRY FRONTIERS 9: (10) pp. 2797-2807., 2022].

Part of the results were shown on a poster at the IUCR conference (14-22. 08.2021, Pague, Czech Republic) and I gave a lecture at the Conference of the Department of crystallisation and drug formulation (08-09. 09. 2022. Pécs, Hungary).

4.2. Understanding the interaction of carboxyl and amine classical API functional groups lead us to the study the 1-cyclohexylethylammonium 2- and 4-chloromandelate crystal lattices. We investigated the effect of the size and position of functional groups attached to the chiral carbon atom in chiral recognition processes. The results were published in the CrystEngComm which is one of the leading journal of the field of single crystal X-ray diffraction. [Bereczki, L; Zodge, A; Korosi, M; **Holczbauer, T**; De, S; Szekely, E; Bombicz, P., CRYSTENGCOMM, 2021, 31, 5367-5376.].

5. iHOF structures

New metal-free ionic hydrogen-bond assisted organic frameworks were studied in our research group. Metal organic frameworks (MOFs) have opened a new field of research: these new type of compounds are suitable for separation and storage, sensing, heterogeneous catalysis, drug delivery, etc. The discovery of MOFs was followed by the new covalent organic frameworks (COFs) in the line as metal-free analogues, and after that the hydrogen bond assisted organic framework was investigated. We reported porous ionic hydrogen-bond assisted organic frameworks (iHOF). The weak intermolecular forces and molecular inflexibility allow to easily change the size and shape of the framework.

Previously we reported the first iHOF structure (1: 5,5,11,11-tetrabutyl-1,3,7,9-tetraphenyl-4,5,6,10,11,12-hexahydro-5,11- diazadibenzo[ef,kl]heptalene-5,11-diium-bromide). This time, we modulated the original molecule by synthetic help of Dr. Roberta Palkó (Organocatalysis Research Group, Research Centre for Natural Sciences) in several ways: the butyl group was exchanged to hexyl; phenyl group was substituted with CF_3 groups (**Fig. 8.**); quaternary nitrogen part was exchanged to phosphate group. We successfully crystallised 7 different crystals from these new compounds. Six of them resulted in an acceptable final R value in the refinement procedure but for the last one we will need a synchrotron source.

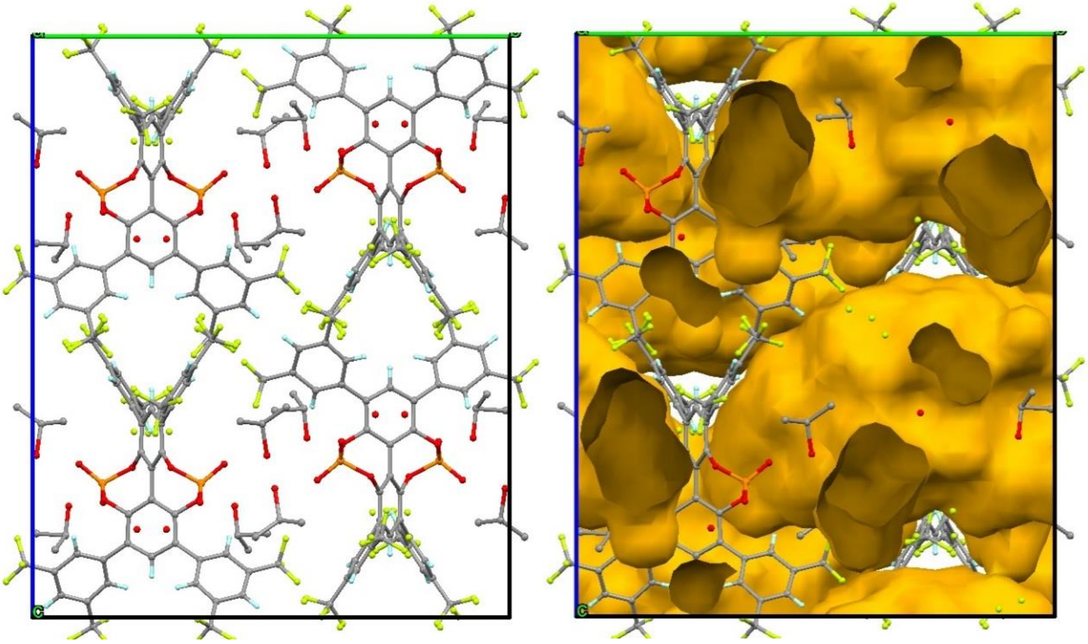

Fig. 8. The unit cell of iHOF crystal showing the framework of organic molecules left figure, and the channels which ensures high porosity (40.8% void/unit cell) is shown on the right figure.

Young participants in the project

Máté Berta MsC student of Eötvös Loránd University (supervised by Tibor Soós), joined to the investigation and performed DFT calculations to calculate intermolecular energies in the case of organocatalysts and borane complexes. Unfortunately, Máté Berta did not finish his studies, so he could not complete the calculations.

Márk Dénes (BME, MSc) was working on new chemotherapeutic metallopharmaceutical candidates. I co-supervised his work together with Nóra May. He successfully finished his studies in 2020.

Kitti Berecz (ELTE, BSc) finished her BSc in the field of API (drotaverine, donepezil and tiofanat-methyl (Dimethyl 4,4’-(o-phenylene)bis(3-thioallophanate)) fungicide) under my supervision in 2019-2020.

Máté Lauer (BME, MSc) are working on the field of silole and silolide rings synthesis under the supervision of Ilona Kovacs. He performed crystallisations and SXRD measurements under my supervision between 2019-2020.

Dávid Lovasi, MSc student of ELTE finished his MSc work in the field of borane complex catalysts under my co-supervision with Tibor Soós. Dávid Lovasi finished his thesis in 2021.

Dalma Gál (BME, BSc) was working on the field of metal bis((di-tert-butylphosphaneyl)methyl)-l2-phosphane complexes under the supervision of Ilona Kovacs. I participated in her education as a consultant. She won a special Students' Scientific Conference award (BME TDK, különdíj, 2020). The synthesised stable compound are investigated under pressure and non-ambient conditions.

Balázs Szatmári synthesizes diketonato-silole compounds under the supervision of Ilona Kovacs. The SXRD investigations of the synthesised compounds have been performed under my leadership as a consultant.

Rita Dobszay, (ELTE, BSc) has also joined to our group and finished her BSc work under my co-supervision (with Gábor London), in the field of the charge transfer complexes in 2021.