# STRUKTURA 2009

## Park Hotel, Hluboká nad Vltavou, 22. 6. - 25. 6., 2009

## Lectures - Monday, June 22

### L1

# STEREOCHEMISTRY OF COMPLEXES OF LANTHANIDE IONS FOR MEDICINAL USE: RELATIONS BETWEEN STRUCTURE AND FUNCTION

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Polyazacycles with coordinating pendant arms are superior ligands for lanthanide ions [1,2]. Polydentate ligands, such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H4dota) and similar ligands, form thermodynamically and kinetically stable complexes even with labile metal ions such as the trivalent lanthanides [2]. Properties of such ligands have been investigated when designing magnetic resonance imaging (MRI) contrast agents [3] based on Gd$^{3+}$ and diagnostic/ therapeutic radiopharmaceuticals utilising metal radionuclides such as $^{90}$Y, $^{64,67}$Cu, $^{111}$In, etc. [4]. In search for other ligands with similar or better properties than common acetate derivatives, research has also been focused on synthesis and investigation of azamacrocycles with phosphonic [5] or phosphinic [6] acids groups on pendant arms.

This lecture is focused on a stereochemistry of cyclen derivatives containing acetic acid pendant arms, methylphosphonic or methylphosphinic acid pendant arms and the similar derivatives are also included in consideration.

All of the structures show that the all H4dota-like ligands are octadentate coordinated to a lanthanide(III) ion, i.e., forming O4 and N4 planes that are parallel and have mutual angle smaller than 3°, even at cases of unsymmetrical ligands [7]. The lanthanide(III) ions lie between these planes, closer to the O4 base than to the N4 plane. All of the structures present the lanthanide(III) complexes in their twisted-square-antiprismatic configuration (TSA‘ – CN8) with or in square-antiprismatic configuration (SA‘ CN8). The coordination shells can be fulfilled by one water molecule over the center of the O4-square; the configurations TSA with CN9 and SA with CN 9 are thus obtained.

In view of potential utilisation of the complexes as contrast agents, an important feature of these structures is the position of the water molecule. The changes in the coordination of water molecule in the the type of complexes depend on the geometry of the O4 plane as it follows from Chart 1.

We found [8] that for the decision on whether water molecule can or cannot be coordinated (change of CN from 8 to 9), a crucial point seems to be the O – Ln – O angle as shown in Chart 1 (angle ). If the value of angle is lager than 131°, coordination of water molecule is possible and the configurations TSA or SA, both with CN 9, are observed; if it is smaler, the space above the O4 plane is too small for the coordination shell expansion. The configurations TSA‘ or SA‘ with CN 8 are hence observed in these cases. It is expectable that structures with CN 9 will be more preferred for larger lanthanides [8]. But the possibility to enlarge the coordination number (CN) does not depend only on is not an ionic radius of metal ion.

The distance between N4 and O4 planes d (see Chart 1) is another important stereochemical parameter. These values are depicted in Fig. 1 and they are almost independent

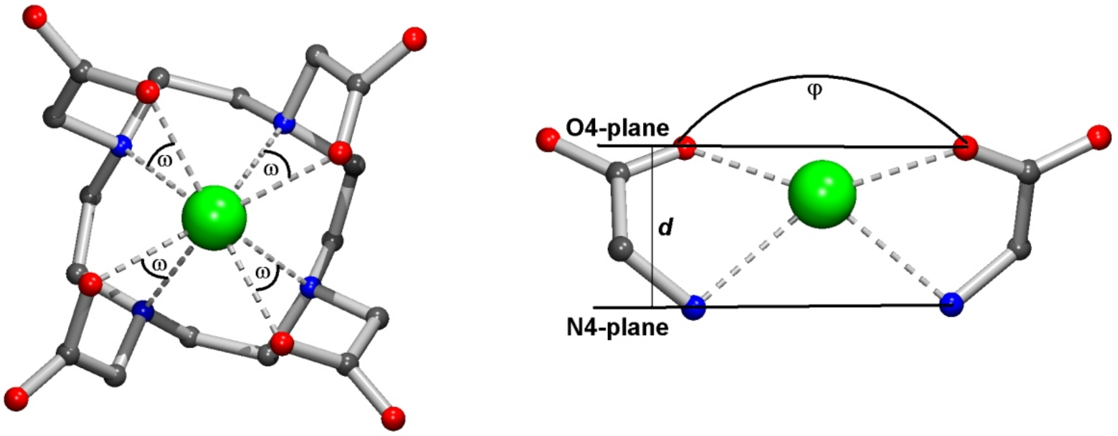

**Chart 1.** Schematic Drawing of the Complexes with the Depicted Structural Parameters : Twist Angle , Opening Angle , O4-plane, N4-plane, and theirs distance *d*.

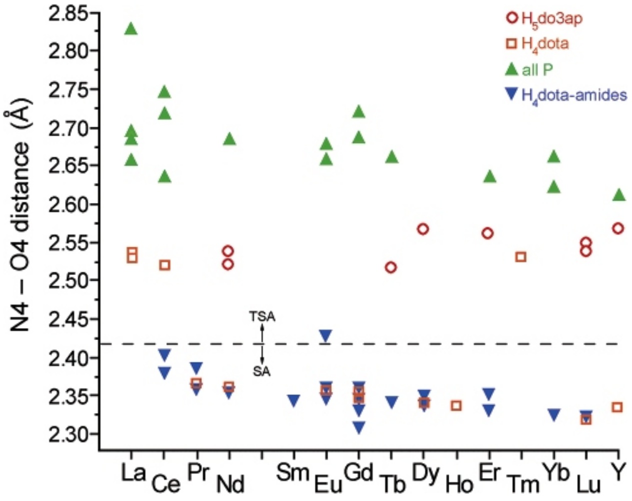

**Figure 1.** Dependence of distance between the O4 and N4 planes in complexes of H4dota-like ligands on the lanthanide: H5do3ap (open red circles), H4dota (open orange squares), ligands with four phosphorus atoms (full green triangles), and H4dota-amides (full blue triangles) (Fig. from [7]).

on lanthanide radius. From the figure, it is clear that the distance found for all phosphorus derivatives are in the range 2.63–2.82 Å. The distances observed for the H$_4$dota and H$_4$dota-tetraamide are split into two groups. The H$_4$dota complexes of La(III), Ce(III), and Tm(III) with the value of ca. 2.5 Å correspond to the TSA (La, Ce) or TSA‘ (Tm) geometry, and the other lanthanide(III) complexes with the value of ca. 2.3 Å conform to the SA arrangement. As shown above in the plot (Fig.1), H$_5$do3ap complexes (ligand with both carboxyl- and phosphorus pendant arms) exhibit the distance of ca. 2.5 Å and, thus, follow the range of H$_4$dota complexes with the TSA and TSA‘ arrangements (with and without a coordinated water molecule, respectively).

We can also distinguish two main point cluster in a (non-depicted there!) plot of the distance between N4 and O4 planes as a function of twist angle (see Chart 1): a compact high-density cluster ( *36°- 40°; distance of the planes near 2.35* Å) corresponding to the SA isomer and a scattered cluster ( *22°- 32°; d 2.5* Å – *2.75* Å) containing two groups belonging to the TSA isomers. The arrangement of the points indicates that the structure of the TSA isomers is not as rigid as that of the SA isomers, being much more influenced by some other interactions. The comparison indicates that the TSA vs SA isomer preference is based on the geometry of the donor atom cavity, which is defined by the ligand, and the size of a lanthanide-(III) ion. The geometry and resulting size of the cavity in complexes of non-phosphorus H$_4$dota-like ligands can be governed only by rotation of the pendants. This rotation leads to the different values of distances d. The SA arrangement should be preferred because of the lower repulsion of the donor atoms. Large lanthanide ions such as La(III) and Ce(III) enforce a larger cavity and thus the N4-O4 distance of 2.5 Å or higher and the formation of the TSA isomer are mostly required for their complexes. As the radius of the Ln(III) decreases, the ion moves to the N4 plane, as was documented in [8]. For non-phosphorus H$_4$dota-like ligands, the shorter distance between the planes is adequate for the Ln(III) after Ce, and thus, the formation of the SA isomer is preferred.

In phosphonic and phosphinic acid derivatives, the pendants show a different geometry resulting from the tetrahedral arrangement of the donor groups, and in addition, the C-P and O-P bonds are longer than the C-C and O-C in the acetate pendant. Therefore, the ligands even with only one phosphonic acid group prefer longer distances O4-N4 planes and the formation of TSA isomer. The ligand cavity in TSA isomers of the small lanthanides is not rigid, as the plot twist angle ů vs distance d between N4- and O4- planes demonstrates.

Plots mentioned above for a number of Ln(III) complexes shows that the arrangement of the TSA isomers is flexible but the higher distance from O4-plane to Ln(III) can induce smaller value of openning angle (see Chart 1) and the coordination shell expansion is more difficult. On the other hand, the arrangement of the SA isomers is rigid but the Ln(III) ion is located nearer to O4-plane and the coordination shell expansion is favoured. Complexes of mono- and diphosphorus [9] acid derivatives make just a borderline between complexes of ligands with acetate pendants and phosphorus acid pendants.

The design of new MRI contrast agents should consider that the exclusive formation of the complexes with the more flexible TSA configuration might lead to a too-long Gd-O$_w$ distance, thus decreasing the overall relaxivity[10]. The coordination of water molecule is easier for more rigid SA isomers but slower water exchange leads to decreasing the overall relaxivity.

The stereochemical analysis of coordination polyhedra in lanthanide complexes with H$_4$dota-like ligands can demonstrate the effect of even slight structural differences on the design of new MRI contrast agents.

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**SL1**

# STRUCTURE TYPES IN THE INORGANIC CRYSTAL STRUCTURE DATABASE ICSD

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Inorganic Crystal Structure Database (**ICSD**), developed and maintained by Fachinformationszentrum Karlsruhe, represents a basic structural database of inorganic compounds. The ICSD [1] comprises such a comprehensive collection of more than 100,000 determined crystal structures of inorganic materials (including intermetallic compounds and oxalates). It contains all available crystallographic data of those crystal structures that have been published since 1913. The editorial team continuously extracts and abstracts the original data from over 80 leading scientific journals and additional 1,900 scientific journals. The ICSD is updated twice a year, each time adding approximately 3,000 new records. The entries are tested for formal errors, plausibility and logical consistency. The data are stored as published; they are not being standardized.

Since 2005, FIZ Karlsruhe began to introduce structure types into ICSD database [2]. The whole idea of structure types is based on non-modular categories of similarity between inorganic crystal structures defined in the IUCr report [3]. The two most important of them – isopontial and isoconfigurational structures – proved to be sufficient to serve as theoretical concepts in introduction of structure types into the ICSD database. The main problem of the assignment of structural types is the subdivision of isopontial structures (i.e. structures with equal space groups and Wyckoff-sequences describing occupied atomic positions) in several, well-defined structure types. For this subdivision the following criteria are used: axial ratio $c/a$, ß range, crystallographic composition (ANX formulae), necessary and forbidden elements. For assignment of most structure types are these criteria sufficient. Only in a few cases also the atomic coordinates must be inspected as an additional criterion [4]. A final criterion that must be fulfilled before a new structure type is introduced into the ICSD is that it must represent the structures of at least three different compounds with the same given structure [2].

In 2008, 59,000 structures out of 100,000 structures in the ICSD were classified into 2500 structure types. The most frequent are spinel ($Al_2MgO_4$), halite (NaCl) and perovskites ($CaTiO_3$ and $GdFeO_3$). Because about 1/3 of the structures in ICSD have no isotypic counterparts, the assignment of structures to certain structure types will be nearly finished [4]. Problems connected with standardization of crystal structure data and other special structural relationships will be briefly discussed, too.

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**L2**

# ADVANCES AND PROBLEMS IN PROTEIN CRYSTALLOGRAPHY

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Since the first protein structure was determined in 1958, the protein crystallography field has undergone enormous progress and development. In this paper, the current state and future development of protein crystallography is reviewed and discussed.

The rate of structure determination has accelerated mainly due to the introduction of new algorithms and computer programs for diffraction data collection, structure solution, refinement, and presentation. The data collection process with current X-ray sources, detectors and computer software is one of the easiest and most automated steps in protein crystallography. Using cryocooled protein crystals reduces the problem of radiation damage, and high intensity synchrotron radiation allows data collection from smaller protein crystals which were previously unusable. Also, phasing procedures have evolved dramatically in recent years. With accurately measured diffraction data, use of anomalous signal for phase estimation is possible. The availability of many different protein fold models allows use of molecular replacement for about half of all structures currently deposited in the Protein Data Bank (PDB). Advances in computer software for model building and refinement as well as computer graphics allow for user-friendly and even automatic model building and refinement.

The achievements of protein crystallography would be very limited without advances in molecular biology techniques of protein preparation and characterization. Many techniques of protein crystallization are now available and used for performing crystallization trials in small volumes and automatic extensive screening of multitudes of initial crystallization conditions. Still, a major bottleneck remains in the preparation of well diffracting protein crystals.

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**SL2**

# NEW GROUP OF X-RAY CRYSTALLOGRAPHY AT THE INSTITUTE OF BIOTECHNOLOGY AS CR

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Institute of Biotechnology AS CR, v.v.i. (IBT) was founded in 2008 with the goal to conduct cutting-edge research on topics suitable for diagnostic and therapeutic applications in human medicine and to serve as a nucleation center of BIOCEV (Biotechnological Center Vestec), the planned biotechnological research center of the Academy of Sciences and Charles University that is to be built at Vestec near Prague by year 2012 with the support of the European Regional Development Funds. Structural biology, namely X-ray crystallography, will be an important methodology at BIOCEV. To nucleate future crystallography group(s) at BIOCEV we have started to build a crystallography laboratory as a part of Dr. Šebo Laboratory of protein ligand engineering at IBT. Currently, the laboratory is fully functional from expression and purification of Prokaryotic proteins to structure refinement. Besides the standard equipment for expression and purification, we have completed a crystallization room operated at 18 °C with stereo microscope Olympus SZX-16 and a diffraction lab with rotating anode Rigaku RU-H3R with image plate detector Raxis4 and cryo-protection Cooler 600 by Oxford Cryosystem. This previously used diffraction system is a generous gift by Prof. Stephen Neidle and Dr. Gary Parkinson from School of Pharmacy, University of London, UK. Staff of the X-ray lab includes four people including a full-time technician. The facility is well equipped for training purposes and for testing diffraction quality of crystals. It is going to be operated as an open facility for any non-profit research group.

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**CL1**

# DIFFRACTED-BEAM ANALYZER WITH MULTIPLE SINGLE CRYSTALS FOR HIGH RESOLUTION PARALLEL-BEAM X-RAY DIFFRACTION

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A single-crystal analyzer is one of the best choices as an X-ray optical device for obtaining high angular resolution and low background intensities in powder and thin-film diffraction experiments. Highest performances regarding the angular resolution and intensities can be obtained when a single-crystal analyzer is coupled with a parallel-beam geometry. In synchrotron radiation (SR) experiments, a high brilliance parallel beam can be obtained from undulator or even bending magnet light sources. A single-crystal analyzer has been commonly used for diffractometer scans at many beam-lines at SR facilities worldwide. Intensity gains in high-angular-resolution and high-speed experiments at several SR facilities around the world have been further multiplied by using multiple-detector systems, each of which consists of several perfect crystal analyzers. With a laboratory X-ray source, diffracted intensities from a single-crystal analyzer are lower than those from a SR source. A popular way to improve high diffraction intensities is to use a rotating anode generator and/or a graded multi-layer mirror. Another way may be the use of a multiple-detector system similar to those presently used in several SR facilities. However, the latter choice makes the diffractometer system more complex and also very expensive.

In the present study, a new high-performance diffracted-beam analyzer consisting of several perfect crystals in a simple and compact device is proposed to increase the diffracted intensities by one order of magnitude compared to those of a single-crystal analyzer. It is commonly believed that an analyzer with high angular resolution cannot be used together with one- or higher-dimension detectors. In this presentation, a new technique using a diffracted-beam analyzer with multiple single crystals together with a one-dimensional silicon strip detector will be presented.

## SL3

# EXPERIENCE WITH THE 1D SILICON STRIP LYNXEYE DETECTOR

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The LynxEye is a 1-dimensional detector for X-ray powder diffraction based on Bruker silicon strip technology capable to detect the X-ray energy from 6 keV to 15keV. The active area of the detector is 14.4 16mm and consists of 192 strips which act as individual detectors. Each strip is 75 m wide and its maximum local count rate is about 650.000 cps, so the maximum global count rate of the detector is about 100.000.000cps. The maximum 2-theta range simultaneously covered is 3.773° in the case of 435 mm measurement circle diameter. It is the maintenance–free detector with no need for counting gas, cooling water or liquid nitrogen. It can be used not only as 1-D detector but as well as 0-D detector with XRD Commander version 2.6 or higher. The 0-D version seems to be useful for the adjustment of the diffractometer and for performing some type of scans like rocking curve or tube scan which are not available in 1-D mode.

The LynxEye detector can dramatically increase of about 200 times the counting statistics respect to a point detector which can bring the following benefits.

- The number of measured powder patterns(standard amount of sample 100 200 mg) may be about 5-10/hour with much better counting statistics respect to a point detector – a higher throughput rate of the diffraction system, improving detection limits of crystalline phases up to 0.1%. Even weak reflections can be identified making qualitative phase analysis faster and more reliable
- Possibility to measure low amount of sample (1 mg 100 g) in a reasonable time from 1 10 hours producing powder patterns suitable for qualitative phase analysis – X-ray microdiffraction
- Possibility to measure sample fixed into capillary (about 20mg) producing almost texture-free powder patterns or to measure unstable compounds
- Possibility to perform temperature dependent measurements to study phase transformation in situ. If the 2-theta range can be limited to 3.773°, the PSD fix scan may be used and statistically reasonable powder pattern collected in 6s, so the sample can be continuously heated with the speed of 10°C/min and results compared with DTA or TGA measurements

1. LynxEye Detector User Manual, Bruker AXS GmbH, Karlsruhe, Germany, May 14, 2008.

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## SL4

# NEUTRON POWDER DIFFRACTION IN NUCLEAR PHYSICS INSTITUTE OF ASCR

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Research team of the Nuclear physics institute has long time experience with the neutron diffraction. The diffraction instruments used up to now were dedicated for studying mainly the strains and stresses in the bulk materials but classical powder diffraction was missing. This free space was filled by the new powder diffractometer that was build and made operational in the second half of 2008.

Nuclear physics institute acquired multidetector bank from the recently closed research reactor in Studtsvik in Sweden. Around this multidetector as a base part new instrument was build that would like to open the neutron powder diffraction technique to large number of new researchers and teams that want to discover advantages of neutron powder diffraction or researches using international neutrons facilities to make first reasonable experiments near home laboratory with easier access.

This new instrument is called MEREDIT (Medium resolution diffractometer) and it is incorporated in to the international NMI3 (Integrated Infrastructure Initiative for Neutron Scattering and Muon Spectroscopy) project. Within this project collaboration and experience exchange with other laboratories and institutions is possible.

The MEREDIT instrument (Fig. 1) is placed at the horizontal channel number 6 in the reactor hall of LWR15 (Light water reactor) in Řež. The default reactor operational power is 10MW and its operation/standby schedule is 3/1 week. The diffractometer consists of two large HUBER goniometer circles. The smaller one provides enough space for placing the different sample environments such as a cryostat, furnace, Euler goniometer, deformation rig, etc. The detector bank is mounted in a moulded neutron shielding made from boron carbide powder in epoxy resin. The bank consists of 35 $^3$He counters with corre-

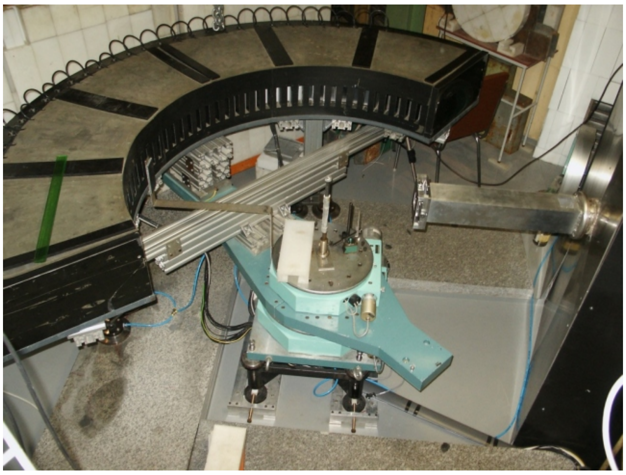

**Figure 1.** MEREDIT instrument: the detector bank of 35 $^3$He counters is moved on air pads. The central HUBER goniometer provides enough space for placing the extensions. The beam size is adjustable by movable slits (middle-right).

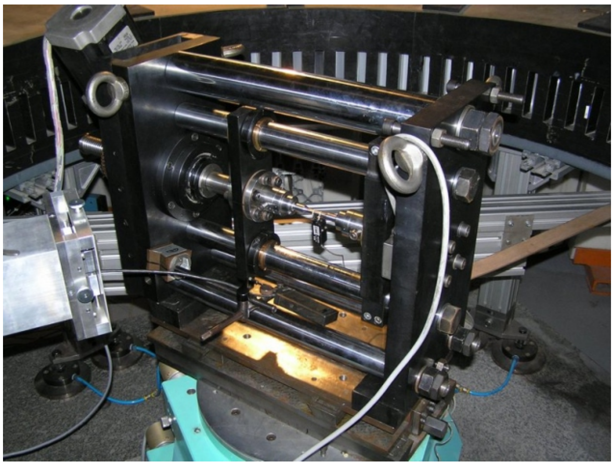

**Figure 2.** *In-situ* deformation measurement with deformation rig on the MEREDIT instrument.

sponding 10’ Soller collimators. They are all individually adjustable and set at angular intervals of 4.00 degrees. The detector bank moves on air pads, which provides together with the stepping motor positioning accuracy down to 0.01 degree in 2 . Diffraction pattern can be collected in the angular range from 2 to 148 degrees in 2 .

Three different wavelengths can be selected using two different automatically exchangeable monochromators. The details about the monochromators and corresponding secondary beam parameters are given in the Table 1.

**Table 1.** Monochromators and secondary beam details

| **Monochromator** | **Reflexion** | **Wavelength (Å)** | **Minimum d/d (x10$^{-3}$)** | **Neutron flux (n.cm$^{-2}$.s$^{-1}$)** | **Beam size** |
|---|---|---|---|---|---|
| 3 bent Si<br>single crystals | 422 | 1.271 | 3.9 (at 56 °2 ) | ~8.8 $^{5}$ | 2 4 mm$^2$ |
| | 311 | 1.877 | 4.4 (at 59 °2 ) | ~8.6 $^{5}$ | 2 4 mm$^2$ |
| 3 mosaic Cu crystals | 220 | 1.460 | 4.9 (at 71 °2 ) | ~3.6 $^{6}$ | 42 4 mm$^2$ |

All movable parts are driven by stepping motors and controlled by PC. The data from 35 counters are collected using two 24-channel Tedia cards. All communication and data collection is made with help of the special software ReMeSys (Regulation and Measurement System). This software is under continuous development to provide the best interface for out diffraction instruments and can easily adopt new extensions and experimental needs. The experiment flow is controlled by scripts written in Pascal like language what provide high flexibility needed for automation of complex experiments.

There are several sample environments to enhance the measurement ability of the instrument: vacuum furnace able to cover the measurement from the room temperature up to ~1000 °C; close cycle cryostat operating from room temperature down to ~10 K. For textured samples, it is also possibility to mount up the Euler goniometer. A special deformation rig permits *in-situ* measurements under uniaxial stress/pressure or fatigue cycles (see Fig. 2).

Collaborations with external researchers were established and the first interesting results of diffraction studies of inter-phase strain in the $ZrO_2$/TiCN ceramics (Catholic University of Leuven, Belgium, see Fig. 3) or hydrogen storage materials $ScAl_{0.8}Mg_{0.2}$ (University of Uppsala, Sweden) are ready to be published. By using the deformation rig we studied in collaboration with the Institute of Physic of Materials of ASCR the deformation of TRIP or chromium-aluminium steels. Occasionally the instruments is also used as a testing facility for orientation the single crystals used for development of the new monochromators.

In collaboration with the Faculty of Mathematics and Physics of the Charles University we plane to use this neutron powder diffractometer for study of the magnetic structure of intermetallic compounds.

The MEREDIT instrument has the power to be universal neutron powder diffractometer which provide easy access to the advantages of neutron diffraction technique and the researchers are welcome to try and taste the neutron science in practice.

*Author would like to thank for financial support from Research Centre Rez (MSM2672244501).*

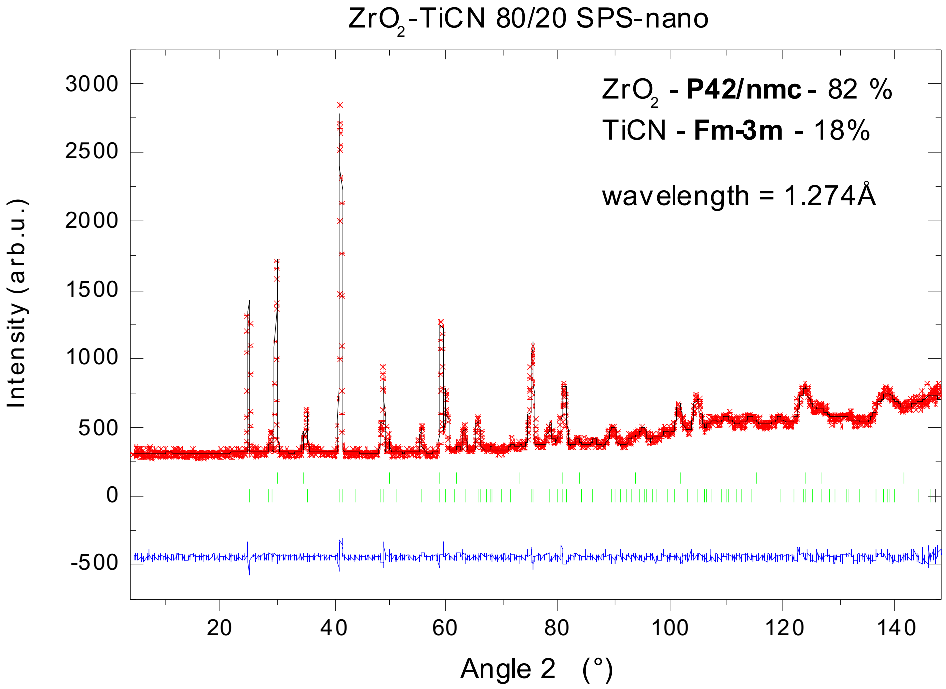

**Figure 3.** Measured and calculated neutron diffraction pattern of sintered $ZrO_2$/TiCN ceramic sample. Pattern was measured with step of 0.05° and delay of 200 seconds per one step (total experiment time 4.5 hour).