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Crystal structure determination of capecitabine from X-ray synchrotron powder diffraction data

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Capecitabine is the first FDA-approved oral chemotherapy for the treatment for some types of cancer, including advanced bowel cancer or breast cancer. Capecitabine is 5-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine, and *in vivo* is enzymatically converted to the active drug 5-fluorouracil. Crystal structure determination of capecitabine was not apparently reported yet. The crystal structure of capecitabine was determined from high-resolution x-ray synchrotron powder diffraction data using parallel tempering method combined with grid computing technique. Data was collected on synchrotron ESRF in Grenoble on beam line ID31. Capecitabine crystallizes in $P2_12_12_1$ space group, Z=4, with unit cell parameters a=5.21, b=9.52, c=34.79, V=1724. The initial model was generated by AM1 computing method implemented in program MOPAC. The structure was solved in program FOX which was modified for grid computing techniques - FoxGrid. The initial model was restrained with bonds and angles restrains. This reduction allowed the parallel tempering to complete within a reasonable computation time. The most probably result in consideration of chemical validity (crystal packing and hydrogen-bonding pattern) was selected for refinement. The structure was refined in program GSAS. The final refinement, treated molecule of capecitabine as relaxed molecule with bonds and angles restrains, leads to final confidence factors Rp=0.096 and Rwp=0.158. This study was supported by the grant of the Czech Grant Agency (GACR 203/07/0040), grant from the Grant Agency of the Academy of Sciences of the Czech Republic (IAA400500602) and by the research program MSM6046137302 of the Ministry of Education,Youth and Sports of the Czech Republic.

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Structure solution of low temperature simvastatin polymorphs from synchrotron powder diffraction

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Simvastatin is a semisynthetic drug used for hypercholesteromia treatment. Since the changes indicating low temp. phase transformations were observed by lab. powder diffractometers and ss NMR, the more precise measurement by synchrotron radiation was done. Data were collected on ESRF synchrotron source, beam line BM01B. At the first the data at room temperature corresponding to the already published simvastatin structure were measured. Scans done during cooling indicated two phase changes, the first one occurring at approx. 261 K and a second one at approx. 223 K. The first high-res. data measurement was done at 258 K. At this temperature simvastatin crystallizes in $P2_12_12_1$ group, Z = 4, with cell parameters a=6.087 Å, b=16.709 Å, and c=23.135 Å. This is almost identical with the room temperature phase exhibiting the same space group and lattice parameters a=6.128 Å, b=17.296 Å, and c=22.469 Å. The restrained structure refinement in GSAS indicated, the differences in intensities are related to side chains conformations rearrangement only. The second high-res. data measurement was done at 150 K. At 150 K simvastatin crystallizes in $P2_1$ space group, Z = 4, with unit cell parameters a=6.024 Å, b=16.220 Å, c=23.477 Å, and β=89.07°. The structure is similar to the higher temperature ones, but the symmetry is lower with 2 molecules in the asymmetric unit cell. It was possible to refine the structure in GSAS by using the hi-temperature phase as staring model and permitting the independent refinement of the two molecules in the asymmetric unit cell. Acknowledgements: This study was supported by the grant of the Czech Grant Agency (GACR 203/07/0040) and by the research programs MSM6046137302 and 2B08021 of the Ministry of Education, Youth and Sports of the Czech Republic.

Keywords: simvastatin, powder diffraction, structure determination

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Ab-initio structure determination of Pb-sulfonamide complexes from powder diffraction data

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1,2-benzenedisulfonamide derivatives are known to extract Pb ion under the presence of an organic base, which deprotonates the sulfonamide nitrogens to coordinate to Pb ion. A new derivative, N,N'-Di-(2-CarboxyMethoxy-3-Thiophene-1,2-Benzenedisulfonamide(CMTB), was synthesized and extraction behavior was investigated. CMTB turned out to be able to extract Pb ion without any organic base. So the crystal structure of Pb-CMTB complex is interesting, but it is hard to obtain the single crystal because Pb-CMTB complex precipitates immediately when CMTB solution is contacted with Pb ion solution. Then the crystal structure of Pb-CMTB was solved by powder diffraction data. Powder diffraction data was collected at BL19B2/SPring-8 using Debye-Scherrer camera. The wavelength of the incident X-ray used was 1Å. Indexing of the pattern was performed with program TREOR and initial crystal structure was obtained with program FOX. Rietveld refinement was performed with program Rietan-FP. Pb-CMTB complex crystallized in the orthorhombic space group Pbcn, with cell parameters a=16.254, b=11.793, c=10.875Å. Final reliability factors of Rietveld refinement were R_p = 0.058, R_{wp} = 0.080. The crystal structure of Pb-CMTB complex revealed that Pb ion was surrounded hemispherically by one CMTB molecule. Pb ion was coordinated to deprotonated two sulfonamide nitrogens and in addition, two carbonyl oxygens of 2-carboxymethoxy-3-thiophene moiety sandwiched Pb ion from the equatorial position. In this poster, crystal structures of Pb complexes with CMTB and some 1,2-benzenedisulfonamide derivatives are presented.

Keywords: *ab-initio* powder sructure determination, metal coordination complexes, synchrotron powder diffraction