Advanced Structural Analyses by Third Generation Synchrotron Radiation Powder Diffraction

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Abstract. Since the advent of the 3rd generation Synchrotron Radiation (SR) sources, such as SPring-8, the capabilities of SR powder diffraction increased greatly not only in an accurate structure refinement but also *ab initio* structure determination. In this study, advanced structural analyses by 3rd generation SR powder diffraction based on the Large Debye-Scherrer camera installed at BL02B2, SPring-8 is described. Because of high angular resolution and high counting statistics powder data collected at BL02B2, SPring-8, *ab initio* structure determination can cope with a molecular crystals with 65 atoms including H atoms. For the structure refinements, it is found that a kind of Maximum Entropy Method in which several atoms are omitted in phase calculation become very important to refine structural details of fairy large molecule in a crystal. It should be emphasized that until the unknown structure is refined very precisely, the obtained structure by Genetic Algorithm (GA) or some other *ab initio* structure determination method using real space structural knowledge, it is not possible to tell whether the structure obtained by the method is correct or not. In order to determine and/or refine crystal structure of rather complicated molecules, we cannot overemphasize the importance of the 3rd generation SR sources.

Keywords: 3rd generation Synchrotron Radiation, powder diffraction, Genetic Algorithm
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INTRODUCTION

Advent of third generation Synchrotron Radiation (SR) has greatly improved the capabilities of X-ray diffraction. Powder diffraction is no exception. A large Debye-Scherrer camera [1] as installed at BL02B2, SPring-8 in order to carry out advanced structural studies by SR powder diffraction. Many SR powder data collected by the camera were analyzed [2] by the advanced analytical method [3], which is the combination of Maximum Entropy Method (MEM) [4] and Rietveld refinements. In this method, Rietveld refinements are performed as a preliminary analysis. In other word, MEM provides an analytical method of crystal structure, which can progress further than Rietveld refinements. As products of such an advanced structural analysis, one can obtain a MEM charge density map. It is consistent with the observed integrated Bragg intensities included in the SR powder data and least biased with unobserved integrated Bragg intensities. If one could measure a SR powder data very precisely with enough resolution, a MEM charge density map derived from the data could be very accurate. It may be said that the advanced analytical method by the combination of MEM and Rietveld refinements utilizing 3rd generation SR powder data is more or less established.

The advantage of *ab initio* structure determination based on 3rd generation SR data seems not very well developed. A part of reason may be due to the fact that *ab initio* structure determination by powder diffraction often stops before very accurate structure refinement is performed presumably assuming any further refinement is not necessary since it is structure determination but not refinement. Because of such an attitude, *ab initio* structure determination is often carry out by laboratory X-ray sources, which can not provide details of whole powder pattern due to the luck of intensities of incident X-ray photons and angular resolution. One has to admit information included X-ray powder pattern collected by an ordinary laboratory X-ray source is much less than SR powder pattern.

The purpose of this study is to demonstrate the importance of 3rd generation SR not only for structure refinements but also for *ab initio* structure determination in the case of relatively complicated organic materials. In order to show

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the practical problems, *ab initio* structure determination and refinement of Prednisolone Succinate ($C_{25}H_{32}O_8$) powder specimen is described.

EXPERIMENTAL DATA

The power specimen of Prednisolone Succinate was sealed in a capillary of 0.4 mm diameter. Then, a SR powder pattern was collected by the Large Debye-Scherrer camera installed at BL02B2, SPring-8 under ambient temperature. The wavelength of incident X-ray was 1.0014 Å and the exposure time was 145 min. The homogeneity of Debye ring was confirmed on Imaging Plate (IP), which is the detector for the camera. Since IP is two-dimensional detector in nature, it is very easy to check the homogeneity of Debye rings. This sometime gives additional advantage to eliminate peaks, which come from impurities. Debye rings of impurities often are very spotty, because impurities exist much less quantities compared with the original sample. The collected data, which will be shown in a later section as Fig. 1 together with the fitting results of Rietveld refinement, shows very sharp independent peaks at low angle regions and details of Bragg intensities undulations at higher angle region. The structural information is included in these undulations.

To have some sharp independent peaks is extremely important to determine unit cell parameters, which is the first step of *ab initio* structure determination. It is possible to perform *ab initio* structure determination of powder specimens by laboratory X-ray sources. But they are all limited for materials with simple structures, for which some independent peaks could be observed in a whole powder pattern collected by laboratory X-ray sources. At this point, there is no doubt that 3rd generation SR source has essential importance. It is obvious that the correct structure can interpret details of Bragg intensities undulations at higher angle region. This will be shown in the next section.

AB INTIO ATRUCTURE DETERMINATION AND REFINEMENT

At first, *ab initio* structure determination of Prednisolone Succinate was done by four steps. First step is cell parameters determination, which was done by *DICVOL04* [5]. The obtained parameters by *DICVOL04* were refined by Le Bail [6] fitting. Prednisolone Succinate is monoclinic and cell parameters are a = 21.1400(2), b = 9.16066(9), c = 24.5891(3) [Å] and β = 98.1456(7) [°]. At second stage, space group is fortunately determined as $P2_1$ unambiguously by observing extinction rule. In many cases, space group could not be uniquely determined at this stage. In such a case, structure determination has to be done for all candidates of space groups. Third step is structure determination process. In the present study, Genetic Algorithm (GA) [7] is adopted. The model structure used in GA is constructed based on relatively similar molecule, which is 6α-methylprednisolone. At fourth step, the crystal structure obtained GA is refined by Rietveld method. Figure 1 shows the fitting results of Rietveld refinement. The R-factors are R_{wp} = 8.56 % and R_I = 19.2 %. The refined structure is shown in Fig. 2. The value of R_{wp} is less than 10 %, which may be normally regarded satisfactory. On the other hand, the value of R_I seems a little too big. It is well know that all the structural information is included in the integrated Bragg intensities. R_I is evaluated based on the integrated Bragg intensities. The discrepancy of two R-factors might suggest that there would be better solution.

In order to study such a possibility, we did further analysis using a kind of MEM analysis, which is slightly different from the ordinary MEM. To have MEM charge densities, the phases of structure factors are calculated from a structure. In the calculation the phases of structure factors, several atoms are intentionally omitted. By omitting these atoms, model bias in the phase calculation, which comes from these atoms, can be partly excluded. MEM charge density distribution obtained in this way will be called omit-MEM map in this study. Omit-MEM map still shows charge densities, which corresponds to the atoms omitted. The atomic positions shown in omit-MEM map are not always same as the structure refined by Rietveld method. Sometime it shows rather different positions. Then, the omitted atoms are placed at the position shown by the omit-MEM map on the viewer program, such as *PyMOL* [8]. In this way, it is possible to perform much more flexible search for a better solution. At the next stage, Rietveld refinement is done to adjust the central position and the direction of the molecule more precisely than the viewer program. The R-factors become R_{wp} = 3.74 % and R_I = 8.15 %, which is much smaller than that of Fig. 1. The observed intensity undulation around 20 ° is now very well fitted by the newly obtained structure and the value of R_I became well below 10 %. At the final stage of the refinement, restrained Rietveld refinement is carried out to adjust atomic positions very slightly. Eventually, the R-factors become R_{wp} = 2.26 % and R_I = 3.47 %. The fitting results of Rietveld program done by this process are shown in Fig. 3. It is concluded that the fitting is satisfactory at all angle

regions and that any further improvement should not be expected. In the consequence, it is reasonable to consider that the structure obtained is correct.

The final structure is shown in Fig. 4, which is quite different from the structure shown in Fig. 2 in both aspects, i.e. crystal structure and molecular structure.

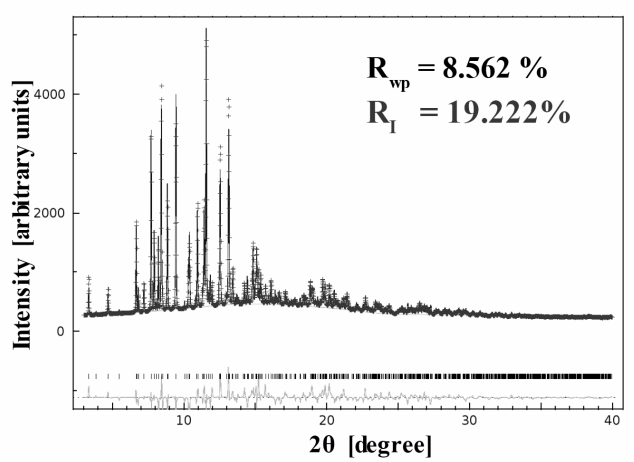

FIGURE 1. Fitting result of Rietveld refinement based on the structure model obtained by GA.

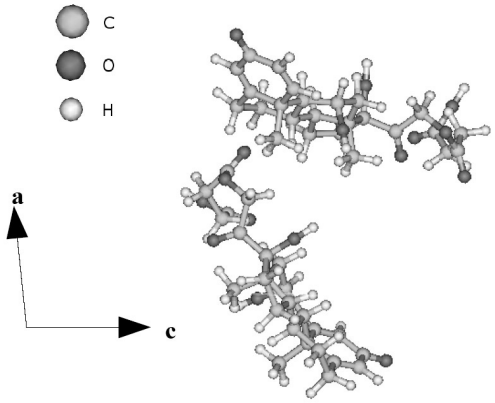

FIGURE 2. The asymmetric unit of the refined structure by Fig. 1.

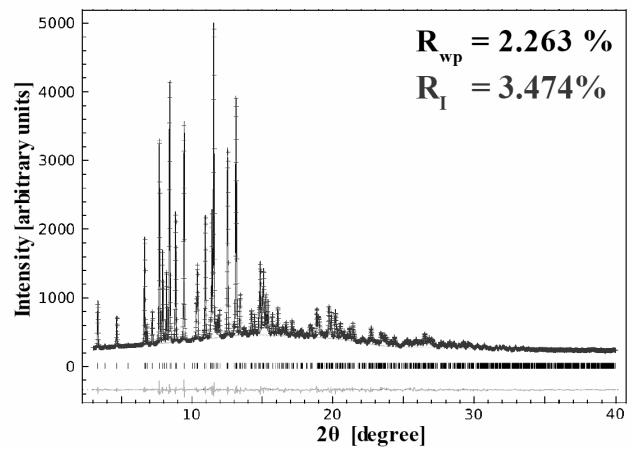

FIGURE 3. The final fitting result of Rietveld refinement.

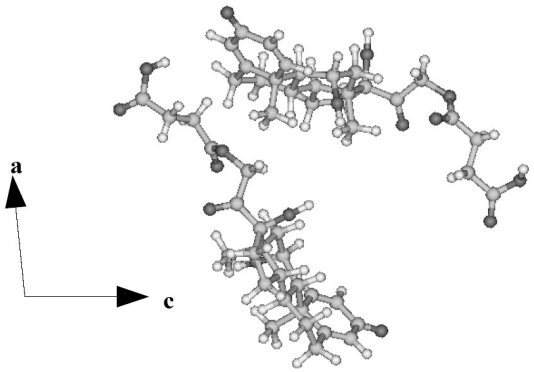

FIGURE 4. The finally refined crystal structure of Prednisolone Succinate (asymmetric unit).

DISCUSSION AND CONCLUSION

The implication of the present study seems rather serious in *ab initio* structure determination by X-ray powder diffraction. Obviously the experimental data taken by 3rd generation SR include much more structural information than the data taken by laboratory X-ray or even 2nd generation SR sources. This is a big advantage of *ab initio* structure determination by 3rd generation SR source. It has to be noted that the crystal and molecular structures, which explain 3rd genaration SR powder data at less than 10 % level in R_{wp} was still not quite right in the present case. It leaves a very difficult problem in *ab initio* structure determination by X-ray powder diffraction. That is how far the experimental data should be analyzed. It of course depends on how complicated structure to be solved. In the present case, the correct structure is obtained when R_I becomes less than 10 %. In R_{wp}, which should be influenced by many factors, such as background level, the value happened to be less than 4 %.

One thing is certain. Until the satisfactory refinement of an accurate experimental powder data, which include enough structural information, is done, it is not possible to tell whether the structure obtained is correct or not. Generally speaking, structure refinement process, such as omit-MEM or Rietveld, is much more time consuming compared with structure determination process, such as GA. There is no guarantee that the structure obtained so-called structure determination process is basically correct. Therefore, an accurate structure refinement utilizing, for example, omit-MEM has to be done to make R_I as small as possible, though an accurate refinement is time consuming and may not be suitable for automatic analysis by a computer program at the present stage.

The present study seems suggest that *ab initio* structure determination of complicated organic materials, such as medicine, by X-ray powder diffraction can be done at least under two conditions. Firstly, a very accurate powder diffraction data, which include enough structural information, has to be measured. Secondly, the data has to be refined extremely well. In this context, an advanced structure analyses by 3rd generation SR has essential importance in both *ab initio* structure determination and accurate refinements by X-ray powder diffraction.

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