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Crystal structure determining of 7-ADCA based on X-ray powder diffraction

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Abstract Optimum resolution data of X-ray powder diffraction for 7-amino desacetoxy cephalosporanic acid(7-ADCA) were collected from an X′ Pert Pro MPD diffractometer with the setup of 0.01°/s and 0.01° per step. Indexing to the crystal system and searching space group from the diffraction data were conducted by means of the computational crystallography method. The pilot crystal models of 7-ADCA were then refined by Rietveld method to obtain the exact three-dimensional structure. The results show that the crystal structure of 7-ADCA is monoclinic, space group $P2_1$ with unit cell dimensions a=13.50 Å, b=6.01 Å, c =5.91 Å, α= γ =90.00°, β=101.96°, Z=2 and V =469.10 Å^3. The fraction coordinate of each atom in the unit cell is well located and reported.

Keywords: 7-ADCA, X-ray diffraction, modeling, crystal.

Traditionally, crystal structure data can be collected and determined from single-crystal X-ray diffraction. However, in the fields of organic and macromolecular crystallography, it is often difficult or impractical to grow single crystals with suitable sizes and purity. Therefore, it will be benefited from the newly growing analytical tool that combining X-ray powder diffraction based on polycrystalline samples and *ab initio* calculation[1].

7-ADCA is one of the most important intermediates in semi-synthetic beta-lactam antibiotic preparation. The crystal characteristics of 7-ADCA have effects on the isolation and purification of the product[2]. However, there is no reported data about the crystal structure of 7-ADCA. In the present investigation, X-ray powder diffraction for polycrystalline powders of 7-ADCA and molecule simulating were combined to study the crystal structure of 7-ADCA .

1 Material and methods

1.1 Material

7-ADCA polycrystalline powder, with the purity of more than 98%, was supplied by Beta Co., Ltd. of the North China Pharmaceuticals Group, Shijiazhuang, Hebei, China. The chemical name of 7-ADCA (see Fig. 1) was [5-Thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid,7-amino-3-methyl-8-oxo-,(6R,7R)], with the CAS register number of 22252-43-3.

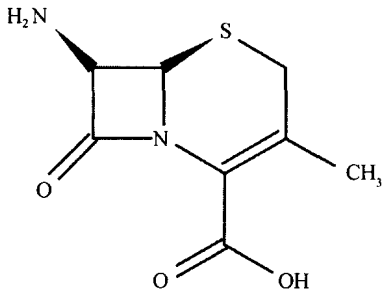

Fig. 1. Molecule structure of 7-ADCA.

1.2 X-ray powder diffraction

X-ray powder diffraction data were collected with an X′ Pert Pro MPD (PANalytical, The Netherlands) diffractometer using monochromatic CuKα1 radiation (λ = 1.5406 Å) at 40 kV and 40 mA. The diffraction patterns were optimized with a step length of 0.01°(2θ) over an angular range 5°—60° (2θ) with a scanning speed of 0.01°/s.

1.3 Block density measurement

0.45 g powders of 7-ADCA were pressed into a pellet under 16 MPa for 1 min. Geometrical sizes of the pellet were measured by a slide caliper to calculate the density of 7-ADCA.

1.4 Crystal structure calculation

Cerius^{2}4.0 (Molecular Simulation Co. Ltd.) was provided by the State Key Laboratory of Polymer Materials Engineering of Sichuan University, the hardware platform was SGI workstation.

2 Results and discussion

2.1 High resolution pattern

While high resolution X-ray diffraction data are ordinarily collected by synchrotron diffractometer in US and European countries[3], distinct data (including peak positions and peak intensity) obtained by universal X-ray powder diffraction contribute practical value to researchers in most cases. Experimental XRD pattern of 7-ADCA after smoothing and background subtraction is shown in Fig. 2. From Fig. 2, it can be seen that the main peak intensities are strong and the peak positions are obvious, so it is fitted for powder indexing.

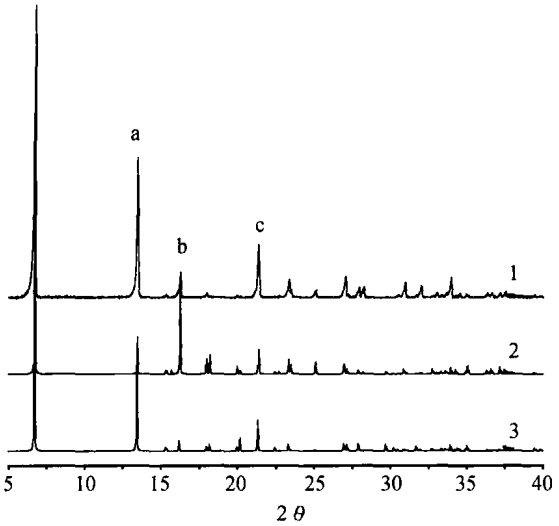

Fig. 2. Experimental XRD pattern versus simulated patterns. 1, Experimental pattern; 2, simulated pattern without refinement; 3, simulated pattern after refinement.

2.2 Powder indexing and space group determination

Peak selection had a marvelous influence on the result. After automatic peak selection with omitting those intensities under 2% of the strongest peak, possible crystal structures of 7-ADCA indexed from the X-cell module[4] are listed in Table 1. The results of manual peak search considering the weak peaks in low angle are shown in Table 2. The extreme differences can be seen from the two tables and indicate the importance of peak selection.

2.3 Powder Solve

The pellet size used in density measurement was 0.26 cm high and 1.27 cm in diameter, and the approximate density of 7-ADCA was about 1.36 g/cm^3. As the number of molecules in each unit cell was integer, the density differences could be easily perceived among different space groups with the same lattice parameter, and density could be critical to eliminate a great deal of unfitted spaces groups in the indexing results. According to the symmetry and cell volume, the calculated crystal intensities of space groups PBCN, IBA2, PMNA, IMA2 and IMMA in Table 1 were all larger than 2.60 g/cm^3, while the intensities of space groups $P2_1$ and P2 were 1.52 g/cm^3 and that of P1 was 1.45 g/cm^3 which were close to experimental intensity (the deviation may be caused by cavity in the pellet). So the monoclinic crystal system with space group $P2_1$, P1 and triclinic crystal system with space group P2 may be the possible crystal structures.

The Powder Solve was carried out to search the possible special arrangement to determine the positions

Table 1 Possible crystal structures of 7-ADCA indexed from automatic peak search

The best space groups of 7-ADCA										
No.	FOM[a)]	System	a (Å)	b (Å)	c (Å)	α (°)	β (°)	γ (°)	Volume (Å^3)	Space group
1	968	monoclinic	13.4873	6.0097	5.9081	90	101.91	90	468.57	$P2_1$
2	231	monoclinic	13.4886	6.0574	5.865	90	101.76	90	469.15	P2
3	186	orthorhombic	4.2067	26.4077	9.8183	90	90	90	1090	PBCN
All possible space groups of 7-ADCA										
No.	FOM[a)]	System	a (Å)	b (Å)	c (Å)	α (°)	β (°)	γ (°)	Volume (Å^3)	Space group
1	968	monoclinic	13.4873	6.0097	5.9081	90	101.91	90	468.57	$P2_1$
2	953	monoclinic	13.4873	6.0097	5.9081	90	101.91	90	468.57	P2
3	978	triclinic	13.3658	4.3949	4.23	94.7	98.263	92.68	244.64	P1
4	186	orthorhombic	4.2067	26.4077	9.8183	90	90	90	1090.7	PBCN
5	308	orthorhombic	26.3914	4.2064	12.024	90	90	90	1334.8	IBA2
6	175	orthorhombic	26.4077	9.8183	4.2067	90	90	90	1090.7	PMNA
7	287	orthorhombic	26.3914	12.0238	4.2064	90	90	90	1334.8	IMMA
8	287	orthorhombic	26.3914	4.2064	12.024	90	90	90	1334.8	IMA2

a) FOM = Figure of merits.

Table 2 Possible crystal structure of 7-ADCA indexed from manual peak search

No.	FOM	System	a (Å)	b (Å)	c (Å)	α(°)	β(°)	γ(°)	Volume (Å^3)	Space group
1	1060	monoclinic	13.4951	6.009	5.9223	90	101.997	90	469.76	$P2_1$

and conformations of molecule groups in the unit cell[5].

2.4 Rietveld refinement

The results obtained in Powder Solve step should be further improved by Rietveld refinement according to the experimental X-ray diffraction pattern. In this step, various parameters including cell parameters, atomic fraction coordinates and bond parameters, etc., were optimized simultaneously to get the optimum crystal structure. Experimental XRD pattern and simulated patterns are shown in Fig. 2. It can be seen that the peak intensities and positions are almost the same between the experimental pattern and the Rietveld refinement treated pattern. The final Rwp of 14.95% was acceptable[6].

The crystal structures with space groups P2 and P1 were also refined. Their final Rwps were 25.42% and 39.18% respectively, which were much larger than that of the space group $P2_1$. The simulated XRD patterns of 7-ADCA with space groups of P2 and P1 were both different from the experimental XRD pattern (see Fig. 3), and the heterogeneity could be reflected markedly between the real structures and the simulated models. From these differences, the crystal structures with space group P2 and P1 should be excluded.

Therefore, 7-ADCA of the experimental sample could be determined as monoclinic system and space group $P2_1$. The unit cell dimensions after refinement were a=13.50 Å, b=6.01 Å, c=5.91 Å, $\alpha = \gamma$ =90.00°, β=101.96°. The cell volume was 469.10 Å^3 and each crystal cell had two 7-ADCA molecules. The final three-dimensional structure, atomic number and atomic coordinates are shown in Figs. 4 and 5, and Table 3.

3 Conclusion

(1) After optimizing measurement parameters, rational resolution X-ray powder diffraction data fitted for indirect crystal structure determination could be obtained by routine X-ray diffractometer.

(2) By means of the molecular simulated software Cerius^2, X-ray powder diffraction data of 7-ADCA were indexed to determine the system and space group of its crystal structure. The pilot crystal structures were then refined by Rietveld refinement to obtain the exact three-dimensional structures and the fraction coordinate of each atom in the unit cell. The results show that the crystal structure of 7-ADCA is monoclinic system, space group $P2_1$ with unit cell dimensions a=13.50 Å, b=6.01 Å, c=5.91 Å, $\alpha = \gamma$ =90.00°, β =101.96°, Z=2 and V=469.10 Å^3.

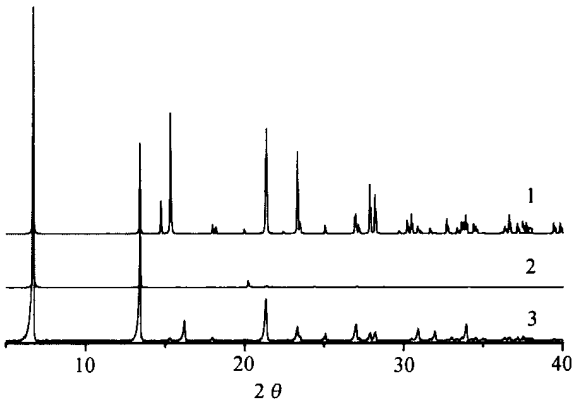

Fig. 3. Experimental and simulated XRD patterns of 7-ADCA with space groups of P2 and P1. 1, Monoclinic P2; 2, triclinic P1; 3, experimental pattern.

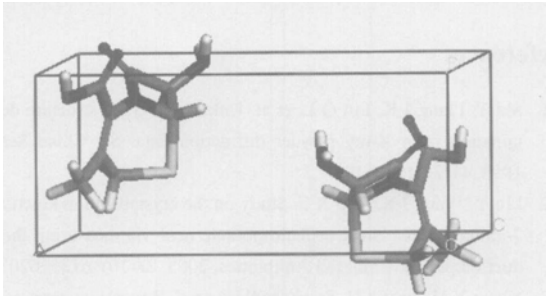

Fig. 4. Three-dimensional structure of 7-ADCA crystal.

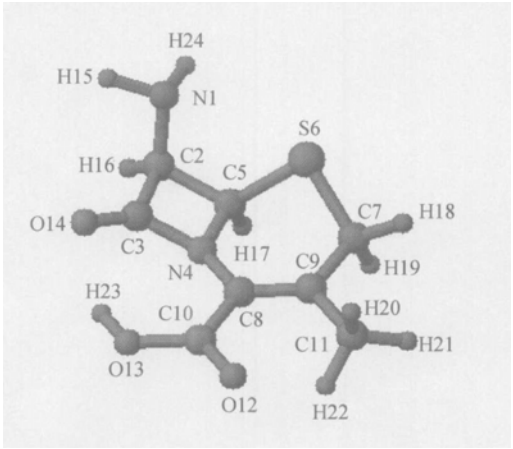

Fig. 5. Atomic number of 7-ADCA.

Table 3 The fraction coordinate of each atom in the 7-ADCA unit cell

Name	*u*	*v*	*w*
N1	0.33001 ± 0.00000	0.47646 ± 0.00016	0.25282 ± 0.00000
C2	0.25506 ± 0.00000	0.34011 ± 0.00007	0.32875 ± 0.00000
C3	0.17035 ± 0.00000	0.44447 ± 0.00030	0.43842 ± 0.00000
N4	0.20386 ± 0.00000	0.32309 ± 0.00001	0.64232 ± 0.00000
C5	0.28917 ± 0.00000	0.21672 ± 0.00025	0.56438 ± 0.00000
S6	0.28510 ± 0.00000	–0.08783 ± 0.00025	0.58654 ± 0.00102
C7	0.15406 ± 0.00000	–0.10171 ± 0.00020	0.63692 ± 0.00086
C8	0.16167 ± 0.00000	0.25720 ± 0.00001	0.83083 ± 0.00000
C9	0.14114 ± 0.00000	0.03574 ± 0.00008	0.84185 ± 0.00000
C10	0.15579 ± 0.00000	0.43738 ± 0.00010	0.99955 ± 0.00000
C11	0.11146 ± 0.00000	–0.08659 ± 0.00004	1.03771 ± 0.00057
O12	0.09417 ± 0.00000	0.38986 ± 0.00001	1.15030 ± 0.00000
O13	0.19983 ± 0.00000	0.61467 ± 0.00027	1.00274 ± 0.00000
O14	0.10213 ± 0.00000	0.57713 ± 0.00060	0.38130 ± 0.00000
H15	0.34643 ± 0.00000	0.61431 ± 0.00030	0.35526 ± 0.00000
H16	0.22235 ± 0.00000	0.22242 ± 0.00030	0.19120 ± 0.00000
H17	0.36365 ± 0.00000	0.27139 ± 0.00061	0.66127 ± 0.00000
H18	0.14045 ± 0.00000	–0.27883 ± 0.00023	0.66281 ± 0.00164
H19	0.10161 ± 0.00000	–0.04648 ± 0.00052	0.47893 ± 0.00015
H20	0.16403 ± 0.00000	–0.22646 ± 0.00020	1.08949 ± 0.00142
H21	0.03546 ± 0.00000	–0.15960 ± 0.00037	0.98047 ± 0.00094
H22	0.11051 ± 0.00000	0.01874 ± 0.00008	1.18787 ± 0.00000
H23	0.09747 ± 0.00000	0.52292 ± 0.00008	1.24721 ± 0.00000
H24	0.30326 ± 0.00000	0.53222 ± 0.00008	0.08832 ± 0.00000

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