

Ab initio structure determination of rofecoxib from powder diffraction data using molecular packing analysis method and direct space method

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Abstract

Crystal structures of a COX-II inhibitor, rofecoxib (*Vioxx*®) were solved ab initio from X-ray powder diffraction pattern using both molecular packing analysis and direct space methods. The X-ray powder pattern was indexed into a tetragonal cell. Packing energies were generated and analyzed in eight most frequently found tetragonal space groups. The two space groups with the lowest total energy, $P4_12_12$ and $P4_32_12$, were used for direct space method with a Monte-Carlo/Simulated Annealing searching algorithm. Structural solutions obtained from direct space method were evaluated using molecular packing energy analysis. The structures solved ab initio from this work were compared to the single crystal structure deposited in the Cambridge Structural Database.

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1. Introduction

Knowledge of crystal structure at the atomic level is usually the first step towards a rational understanding of physico-chemical properties of crystalline pharmaceutical solids. The most reliable and widely used method for obtaining solid state structures is single crystal X-ray analysis. Over the last 30 years, this method has become a routine and straightforward tool for small molecule structure determination. However, for many drug molecules it is very challenging to obtain crystals with sufficient dimensions and quality suitable for X-ray single crystal analysis. Hence, there

has recently been increased interest in applying alternative means to determine solid state structures of pharmaceuticals (Dinnebier et al., 2000; Stephenson, 2000; Giovannini et al., 2001).

X-ray powder diffraction patterns have played an important role in the structural characterization of new inorganic or hybrid materials (Paiva-Santos et al., 2000; Barnes et al., 1997; Burton et al., 2000). Unlike single crystal analysis, X-ray powder diffraction patterns can be readily collected from polycrystalline samples with less effort involved in sample preparation. X-ray powder diffraction patterns, as single crystal X-ray data, are generated from the reflections of crystal planes. The information contained in the powder diffraction pattern is however limited since the reflections from different crystal planes are projected onto a single variable, the diffraction angle,

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and therefore intrinsically overlapped. This intrinsic overlapping of reflection makes traditional methods (Patterson and direct methods) difficult when the system is large and the space group symmetry is low. Pharmaceutical solids are mainly organic crystals in low space group symmetry and typically lack heavy atom scatterers. Thus, powder X-ray diffraction has traditionally been used in the pharmaceutical industry to identify polymorphism and crystallinity.

A different approach for solving crystal structures from powder X-ray diffraction patterns is to generate structure candidates in direct space, thus termed the direct space method (Deem and Newsam, 1989; Reck et al., 1988), and compare the calculated powder patterns to the experimental one. This method requires and takes advantage of knowledge of the connectivity of the atoms a priori. With the knowledge of the molecular bond lengths and bond angles, the key parameter to a successful structure solution is the number of torsional angles, which is usually a smaller number than atom coordinates. This method should generally allow structure determination from lower quality X-ray powder patterns. For pharmaceuticals, the connectivity of atoms is known and the molecular geometry can be deduced from tabulated data or ab initio geometry optimization. The advances in fast computers and search algorithms such as Monte-Carlo/Simulated Annealing (MC/SA; Andreev et al., 1997; David et al., 1998; Putz et al., 1999; Coelho, 2000; Pagola et al., 2000) have made the direct space method a practical alternative to the single crystal X-ray method for pharmaceuticals.

A parallel methodology for obtaining crystal structures without large single crystals is molecular packing analysis using molecular mechanics. This method is used to predict the structure of crystals by energy minimization based on a proper force field. This approach is therefore ab initio and theoretically requires no experimental data other than the knowledge of the molecular structure. However, X-ray powder diffraction patterns provide a reference for evaluating the calculated structural models and can be used to further refine the start model. Various computer programs have been developed based on molecular packing analysis method (Williams, 2002; Gavezzotti, 1997; Holden et al., 1993). Some of the programs are designed to “predict” possible polymorphs based on molecular structures, an example being the method-

ology developed by Gdanitz et al. (1993) and later integrated in the commercial package Cerius² (Chemical Simulation Software Package, Accelrys Inc., San Diego, CA, USA). This methodology incorporates a simulated annealing algorithm to randomly generate thousands of possible crystal structures and then energetically minimize the structures with a force field. This simulation package has been successfully used to study potential polymorphs and predict crystal structures of certain pharmaceutical molecules (Payne et al., 1999a,b).

In this article we report the structure determination of a COX-II inhibitor, rofecoxib, using both molecular packing analysis and direct space X-ray diffraction methods. COX-II inhibitors have attracted wide interest due to their COX-II/COX-I selectivity and reduced gastrointestinal irritation. Many papers have been published regarding the structure of COX-II inhibitors (Plount and Jorgensen, 2000; Desiraju et al., 2000; Luong et al., 1996) including the single crystal structure of rofecoxib (Rekha et al., 2000). However, in this work we tried to disregard the known single crystal structure before the preliminary solutions from the alternative means were obtained. This article therefore is partially a validation of the commercial simulation package Cerius² in which the two methods are integrated, and partially an introduction to a new route of structure determination for pharmaceutical solids.

2. Experimental section

2.1. General procedure

The material used for powder X-ray data collection was obtained from Merck & Co., Inc. (>98% pure), and used without further recrystallization. The sample was sealed in a 0.7 mm special glass capillary tube for X-ray diffraction study. Powder X-ray diffraction data were collected on an Inel MPD X-ray diffractometer equipped with a CPS 120 detector at 35 kV, 30 mA, for Cu K α 1; $\lambda = 1.5406 \text{ \AA}$. A mixture of silicon and silver behenate was used as an external standard. Lattice constants were fitted by the Pawley method (Pawley, 1981) and powder data were indexed by a trial and error algorithm using the computer program TREOR (Werner et al., 1985).

The computation was performed on a SGI Oxygen workstation with a R10000 processor at 250 MHz and an SGI Octane workstation with a R12000 processor at 400 MHz. The molecular packing analysis was performed using the *Polymorph Predictor*¹⁸ and the simulated annealing structure determination using the *Powder Solve*¹⁸. Both *Polymorph Predictor* and *Powder Solve* were incorporated in the molecular simulation software suite Cerius².

3. Computational methods

3.1. Molecular packing analysis

The only inputs required by the molecular packing analysis method are the molecular structure and a force field. In order to have a meaningful packing analysis, the bond distance and bond angles of the molecule need to be as accurate as possible. Moreover, the electrostatics potential (ESP) of the molecule needs to be assigned to appropriate theoretical values as the ESP will be a deciding factor for the calculated energies of different molecular packings. In this work, the molecular electrostatics potential was obtained according to the restricted Hartree–Fock formalism (RHF) at the 6-31G** level with the quantum mechanics program Gaussian92 (Frisch et al., 1993) and the molecular structure was minimized by the force field “Dreiding 2.21” (Mayo et al., 1990).

Polymorph Predictor simulates the packing process for molecular crystals and generates a number of energetically stable structures. There are two main steps in this simulation process: Monte-Carlo packing simulation and energy minimization. The first step, Monte-Carlo simulation, randomly generates many possible structures for a chosen molecule. This simulation involves two phases, heating and cooling, hence termed simulated annealing. The heating phase is to find a starting temperature for the simulated annealing. This starting temperature should be on the one hand high enough so that phase space can be considered as sampled completely randomly, but on the other hand low enough so that the cooling steps are not wasted on making random moves. Two parameters are used in the heating phase: N_accept and Heat_Factor. N_accept is the number of structures that are accepted before it is considered in a random

state. Heat_Factor defines the rate of heating during the attempt to reach the random state. After the starting temperature is reached, the system starts to cool down. The cooling phase is the simulated annealing step in which all possible structures are searched. The rate of cooling is therefore of particular importance as it affects the number of Monte-Carlo moves per temperature unit of the simulated annealing. The parameter that controls the rate of cooling is the Cool_Factor. Reducing the Cool_Factor increases the detail of the search and the total simulation time.

The structures generated by Monte-Carlo simulation are energetically unrefined and therefore subject to energy minimization based on a variety of open force fields. In the minimization step the symmetry of the space group is retained while all degrees of freedom including the bond angle, bond length, and the cell constants are relaxed and minimized. Minimization terminates when the user defined convergence level of RMSF, the root mean squared force, is reached. The force field “Dreiding 2.21” was recommended for *Polymorph Predictor* for systems without metals and hence used in this study. The four important parameters for packing energy analysis are N_accept (15), Heat_Factor (0.025), Cool_Factor (0.001), and RMSF (0.001).

3.2. Powder X-ray direct space method

The rofecoxib molecule fragment used in the direct space method structure determination is the same as the one used in the molecular packing analysis. The X-ray powder pattern was fitted and intensities extracted by the Pawley method using *Powder Fit*, which is integrated in the Cerius² simulation suite. The extracted intensities were used in the simulated annealing program *Powder Solve* for the structure determination. The simulation steps were set to 500,000.

4. Results and discussion

4.1. The compound

Rofecoxib (4-(4'-methyl-sulfonylphenyl)-3-phenyl-2-(5*H*)-furanone, *Vioxx*[®]) is a COX-II inhibitor with only one known polymorph. The optimized molecular structure of rofecoxib is shown in Fig. 1.

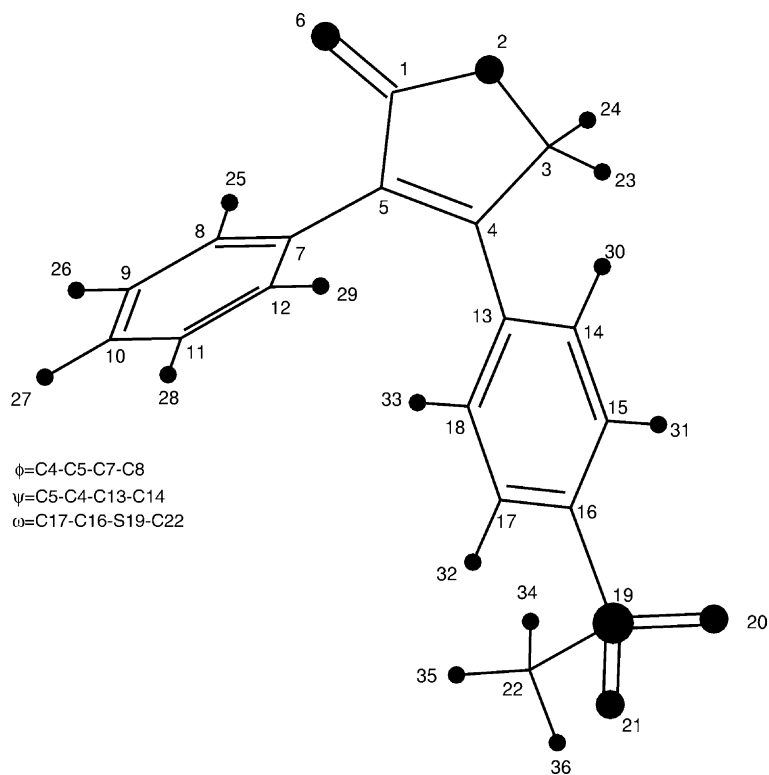


Fig. 1. Optimized rofecoxib structure and its torsion angles. S: ; O: ; H: ; C: stick.

4.2. Structural determination by packing energy analysis

The first stage of the molecular packing analysis is to determine the likely space group(s). Without information from experimental data (for example, an indexed cell by either the X-ray powder diffraction pattern or single crystal X-ray diffraction method), there are theoretically 230 space groups that are possible. It would be tedious and CPU-time consuming to go through all 230 space groups to search for the energetically favorable solutions. Fortunately, in reality over 74.5% of solved single crystal structures that are deposited in the Cambridge Structural Database (CSD) were found in only five space groups, namely $P2_1/c$, $P-1$, $P2_12_12_1$, $P2_1$, and $C2/c$ (Wilson, 1988; Allen et al., 1994). Experimental data, such as X-ray diffraction patterns, optical activity and cell dimensions also help greatly to narrow down the possible space groups.

In the case of rofecoxib, the X-ray diffraction pattern was indexed into a tetragonal cell with cell dimen-

sions $a = 11.386(5) \text{ \AA}$ and $c = 22.942(11) \text{ \AA}$. The indexing was calculated based on 20 reflections and the figure of merit ($M(20)$) is 13. This figure of merit indicates that the indexing is substantially correct (de Wolff, 1968). There is a total of 68 space groups in the tetragonal system. If one analyzes the CSD database for the tetragonal system and sorts the space groups by the frequencies, one finds a cutoff point at 0.1% (Allen et al., 1994). Among the 68 tetragonal space groups, only 8 space groups occupy 0.1% and higher of total solved single crystal structures deposited in CSD. These eight space groups and their occurrence frequencies in CSD are listed in Table 1. Molecular packing analyses in these eight space groups were carried out using the program *Polymorph Predictor*.

In Fig. 2 we show the plot of the total energy per asymmetric unit of the 10 most stable structures for the eight tetragonal space groups studied. Among the first frame solutions, which have the lowest total energies found in their own space groups, $P4_32_12$, $P4_12_12$, and $P4_2/n$ are clearly more stable than the

Table 1
Percentage of the most commonly found tetragonal space groups

Space group	Frequency (%)
$P4_1$	0.118
$I-4$	0.159
$P4/n$	0.101
$P4_2/n$	0.136
$I4_1/a$	0.322
$P4_12_12$	0.264
$P4_32_12$	0.127
$P-42_1c$	0.143

other space groups. Moreover, in these three space groups the most stable structures are all energetically distinguished from the second most stable structures. The cell parameters as well as the densities of the three structures are listed in Table 2. The three structures of space groups $P4_32_12$, $P4_12_12$ and $P4_2/n$ are subsequently used to simulate X-ray powder patterns, which are shown in Fig. 3 with the experimental powder pattern. The simulated powder patterns from the two structures of $P4_32_12$ and $P4_12_12$ are identical and extremely similar to the experimental one while the $P4_2/n$ structure is clearly incorrect.

Crystallographically the two space groups $P4_32_12$ and $P4_12_12$ are different only by the 4-fold screw axis. In $P4_12_12$, the 4-fold screw axis makes a right-hand rotation while in $P4_32_12$ the axis makes a left-hand rotation. The two space groups are therefore chiral to each other. In Fig. 1 one sees that although rofecoxib molecule is not optically active in solution, it is chiral in solid state for the lack of improper axis. The two structures solved from space groups $P4_12_12$

Table 2
Cell parameters and density and energy for the three most stable structures

Space group	a (Å)	c (Å)	Density (g/cm)	Total energy (kcal/mol)
$P4_12_12$	11.41	23.54	1.36	−477.62
$P4_32_12$	11.40	23.62	1.36	−478.51
$P4_2/n$	22.19	6.22	1.36	−470.88

and $P4_32_12$ have identical cell constants, simulated powder patterns, and total energies. As one sees in Fig. 4, which shows the molecular structures of rofecoxib calculated in $P4_32_12$ and $P4_12_12$, the two molecular structures are enantiomeric. The two calculated crystal structures of rofecoxib in $P4_32_12$ and $P4_12_12$ are shown in Fig. 5. In Fig. 5 the coordinates of the $P4_32_12$ cell and the $P4_12_12$ cell are viewed from different direction. As one sees in Fig. 5, the b axis of the $P4_12_12$ cell is pointing to the left and c axis upward; In the $P4_32_12$ cell while the b axis is pointing to the left, the c axis is pointing downward. The two crystal structures can be seen in Fig. 5, neglecting the cell coordinate direction, as related by a mirror plane.

4.3. Structure determination by direct space method from X-ray diffraction data

The X-ray diffraction pattern was indexed and the cell constants known from the molecular packing analysis work. Two space groups, $P4_32_12$ and $P4_12_12$, were identified as having the lowest total energies. It is impossible to distinguish these two space groups by

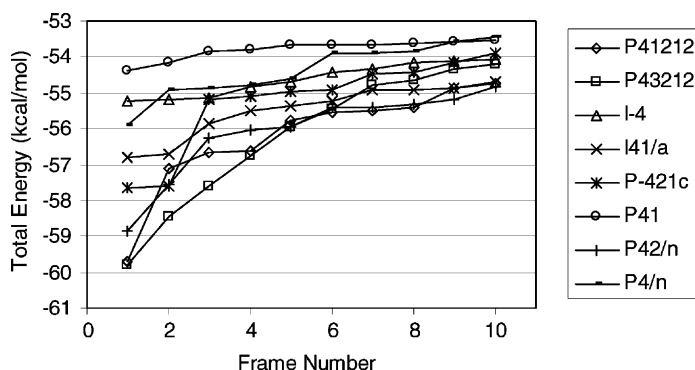


Fig. 2. Plot of total energies for the 10 most stable structures from the molecular packing calculation.

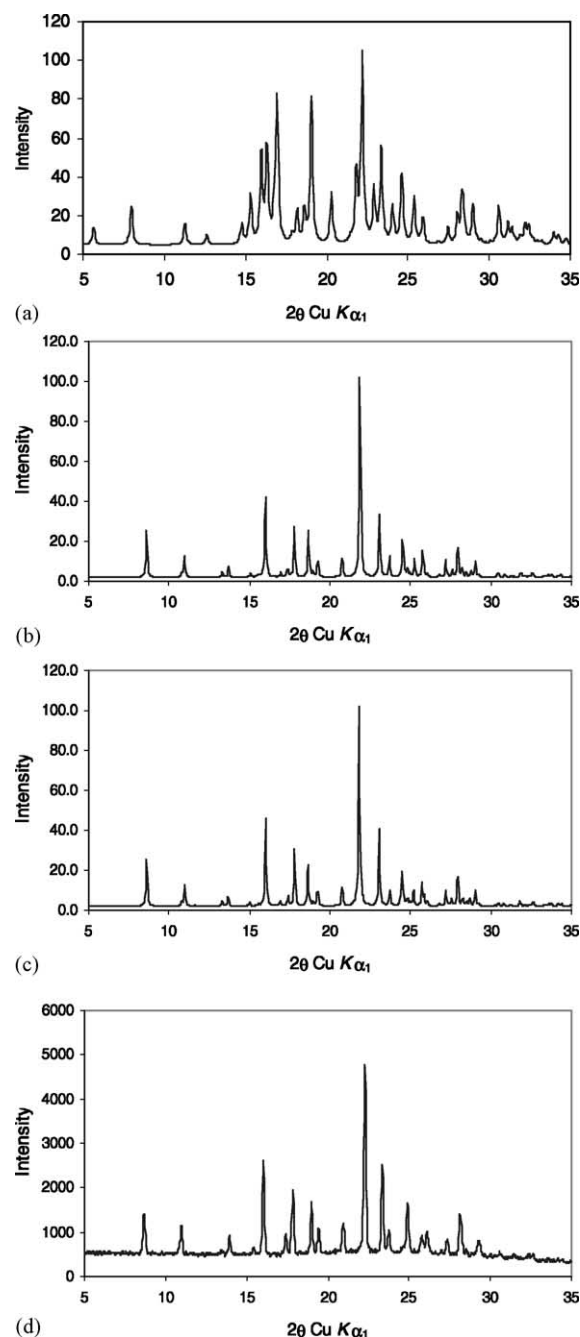


Fig. 3. Calculated powder patterns of rofecoxib based on models generated from molecular packing calculation in space groups (a) $P4_2/n$, (b) $P4_12_12$, (c) $P4_32_12$, and (d) experimental powder pattern.

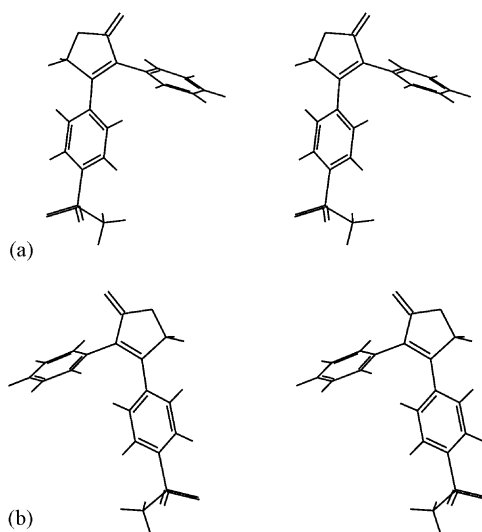


Fig. 4. Stereoviews of rofecoxib molecules obtained from molecular packing calculation in space groups (a) $P4_12_12$ and (b) $P4_32_12$.

powder diffraction data. Hence we decided to solve and report the structures in both space groups.

The rofecoxib molecule fragment was obtained from the one used in molecular packing analyses without modification. Based on the cell volume of 2977.79 \AA^3 , one crystallographically nonequivalent rofecoxib molecule makes the density of the cell

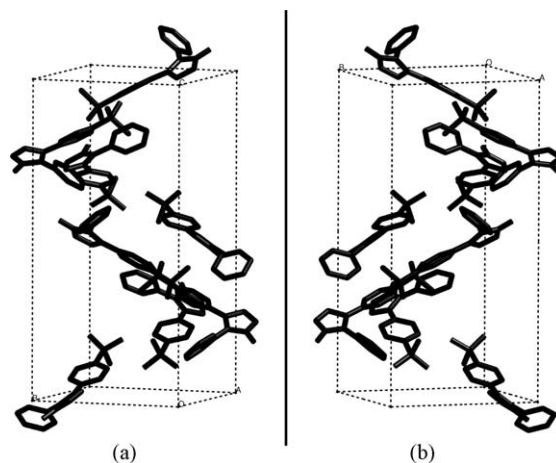


Fig. 5. Crystal structures of rofecoxib calculated using molecular packing analysis method in space groups (a) $P4_12_12$ and (b) $P4_32_12$. Black line between the two structures represents a mirror plane.

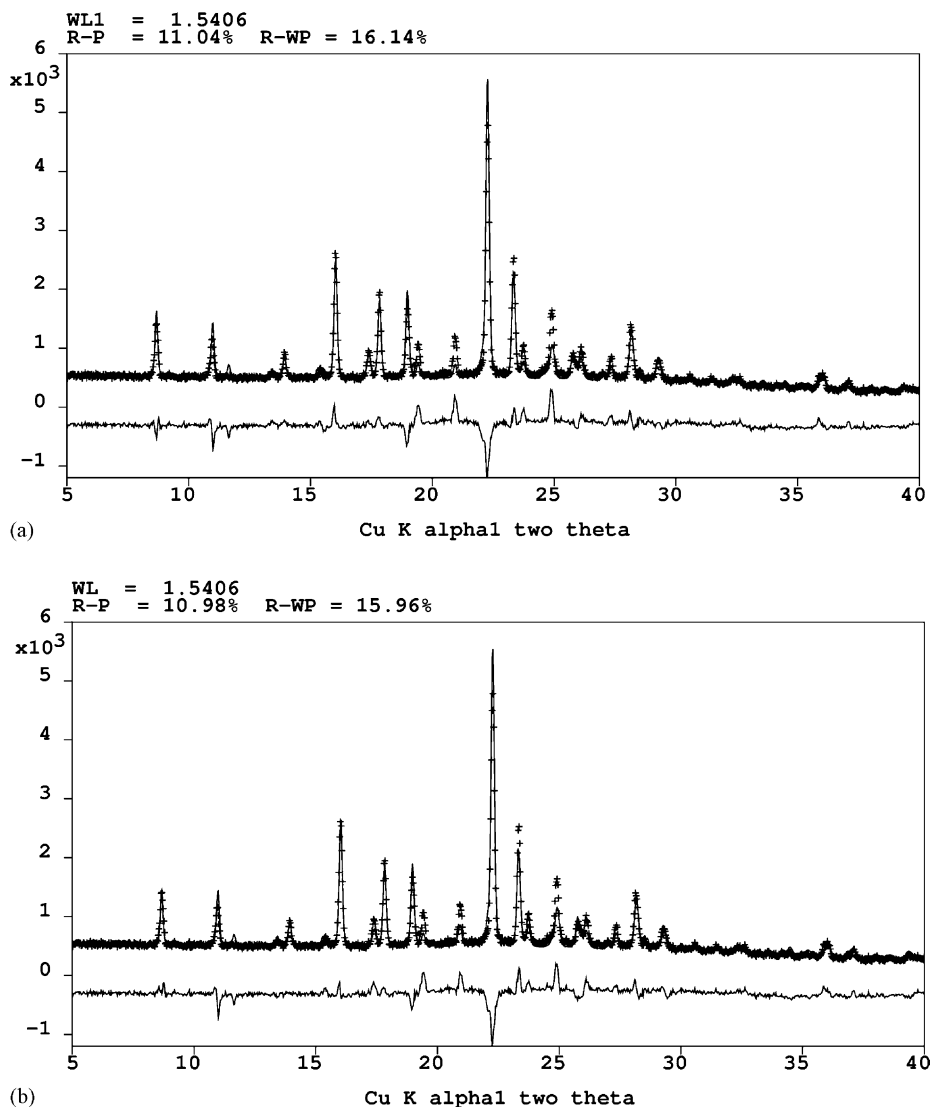


Fig. 6. Observed (+), calculated, and difference (bottom) X-ray powder diffraction patterns of rofecoxib in (a) $P4_12_12$ and (b) $P4_32_12$ using *Powder Solve*.

1.41 g/cm^3 . This is indicative that there is only one crystallographically nonequivalent rofecoxib molecule present in the cell. The rofecoxib molecule has three torsion angles. With one independent molecule in the unit cell, there are totally nine degrees of freedom as three for translation, three for rotation, and three for torsion. This is well within the limit of the MC/SA simulation program *Powder Solve*. The structures in both space groups were solved readily with the

same solutions in five separate solution cycles. The comparison of the experimental powder patterns and the ones generated by the solved structure models is shown in Fig. 6.

The molecular packing in these two solved structures is very similar to that found in the *ab initio* molecular packing analyses. However, a careful examination of the molecular structures obtained from both the direct space method and molecular packing

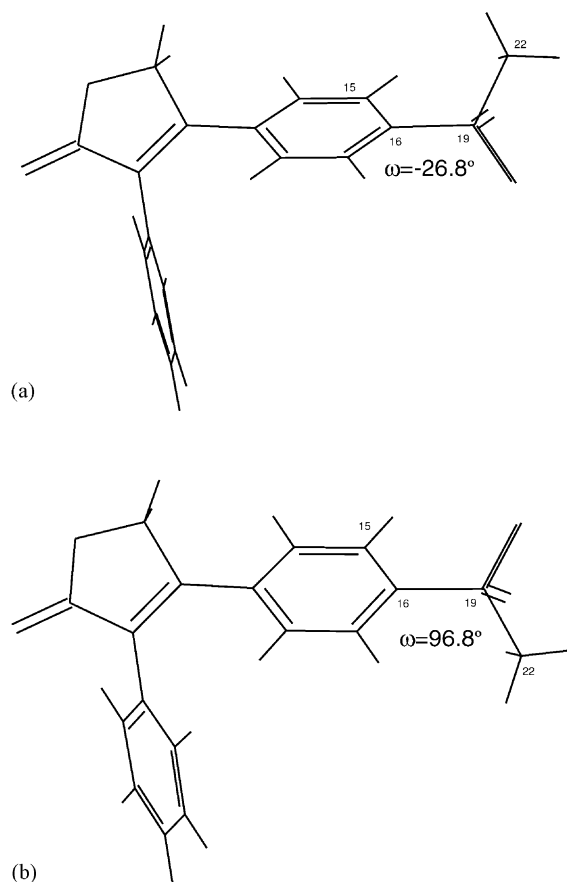


Fig. 7. Molecular structures of rofecoxib in space group $P4_12_12$ obtained from (a) direct space method and (b) molecular packing analysis method using the same starting molecular model.

revealed a difference in the positions of the methylsulfonyl group. The rofecoxib molecular structures calculated in $P4_12_12$ are shown in Fig. 7. The torsion angle ω_1 in the structure obtained from the molecular packing calculation is 96.8° , while in the structure solved from the X-ray powder data the torsion angle ω_1 is -26.8° . For the structures solved in $P4_32_12$, the torsion angle ω_2 found in the molecular packing analysis structure is -97.9° and in the powder X-ray structure is 7.7° . The weighted profile residual values ($R_{wp} = [\sum_i w_i |I_{exp}(\theta_i) - I_{calc}(\theta_i)|^2 / \sum_i w_i |I_{exp}(\theta_i)|]^{1/2}$), 16.14 and 15.96%, are considered acceptable. However, the low R_{wp} value does not mean that the structure solution is necessarily correct. Similarly in X-ray single crystal method, a low overall Reliability

index, R factor, is indicative of the reliability of the refinement, but not a guarantee of the correctness of the solved structure. The bond distances, bond angles, thermal ellipsoids and the space group symmetry all need to be examined carefully in order to evaluate whether the final structure is solved correctly or not. In the direct space method, with the quality of data from Cu radiation generated by a sealed X-ray tube, refinement on the atom coordinates and thermal factors is usually extremely difficult if not impossible. In the structure solution without refinement, the atom connectivity, that is, the bond distances and the bond angles are predecided by the known chemical information. With the restraints on the atom connectivity, it is difficult to determine if the structure solution from the direct space method is correct. However, intramolecular interactions, e.g. hydrogen-bonding pattern, π - π interaction, closest contact, etc. can be used as indications for the reliability of the solution. These interactions can be measured using molecular packing analysis method with an appropriate force field. We calculated the packing energy of solved structures using the force field "Dreiding 2.21" and obtained the total energies for the structures in $P4_12_12$ and $P4_32_12$ as 0.16 and -8.12 kcal/mol, respectively. A second set of packing energy calculation was carried out with the same structures only the methylsulfonyl groups rotated in such a way that the torsion angles ω_1 and ω_2 were set to 96.8 and -97.9° , exactly the same as the ones found in molecular packing structures. This change of torsion angle ω dramatically lowered the calculated total energies for the structures in $P4_12_12$ and $P4_32_12$ from 0.16 and -8.12 to -158.29 and -159.26 kcal/mol, respectively. These results showed that the direct space group method did not locate the conformation of the methylsulfonyl group correctly from the first five MC/SA cycles.

As bond distances and angles are restrained throughout the MC/SA process, it is critical to have correct bond distances and angles to start the MC/SA search. We examined the bond distances of the S=O and S-C bonds of the methylsulfonyl group and built a new rofecoxib molecular model by modifying the S=O and S-C bonds using the standard bond lengths (Lide, 2001). The bond lengths of the methylsulfonyl group in the two molecular models are listed in Table 3. In Table 3, model 1 was the

Table 3
Bond lengths (in Å) of methylsulfonyl group

	Model 1	Model 2
S(19)–C(22)	1.770	1.776
S(19)–O(20)	1.579	1.436
S(19)–O(21)	1.579	1.436
C(16)–S(19)	1.744	1.764
C(22)–H(34)	1.085	1.085
C(22)–H(35)	1.085	1.085
C(22)–H(36)	1.084	1.084

molecular model used for the packing energy analysis method and model 2 was the new model in which the S=O and S–C bond distances were corrected based on the standard bond lengths. With the model 2 as the starting molecular model, the solutions from five MC/SA sequences resulted in the correct conformations of rofecoxib molecules as in the ones obtained from molecular packing analyses. The final R_{wp} of the structures in $P4_12_12$ and $P4_32_12$ are 16.54 and 16.32%, respectively. The torsion angles ω_1 and ω_2 are -78.9 and -114.9° . The two structure solutions are enantiomers to each other as expected.

4.4. Validation of the calculated structures with the X-ray single crystal structure

The reported single crystal structure of rofecoxib was solved in $P4_12_12$. The bond distances, and the torsion angles of the rofecoxib molecules from both the single crystal structure data and this work are listed in Table 4. Fig. 8 demonstrates the similarity of the rofecoxib crystal structures determined by single crystal X-ray diffraction and by the direct space method and molecular packing analyses. The molecular geometry of rofecoxib obtained from the single crystal was used as the molecular fragment in direct space method with the three torsion angles free to rotate. The correct methylsulfonyl conformation was located in all five consecutive cycles with a best R_{wp} 16.00%.

4.5. Conclusion

Structure solutions of rofecoxib were obtained from molecular packing analysis and direct space method

Table 4
Bond lengths (in Å) and torsion angles (in $^\circ$) for rofecoxib

	Direct space method*	Molecular packing*	Single crystal
C(16)–S(19)	1.764	1.740	1.756(3)
S(19)–O(20)	1.436	1.582	1.436(2)
S(19)–O(21)	1.436	1.579	1.433(2)
S(19)–C(22)	1.776	1.768	1.749(3)
C(1)–O(2)	1.350	1.343	1.350(5)
O(2)–C(3)	1.421	1.425	1.434(4)
C(3)–C(4)	1.472	1.478	1.502(4)
C(4)–C(5)	1.411	1.407	1.331(4)
C(5)–C(1)	1.404	1.386	1.490(4)
C(1)–O(6)	1.250	1.249	1.202(4)
C(5)–C(7)	1.410	1.402	1.470(5)
C(7)–C(8)	1.415	1.409	1.383(4)
C(8)–C(9)	1.408	1.409	1.365(6)
C(9)–C(10)	1.406	1.406	1.388(7)
C(10)–C(11)	1.406	1.407	1.383(6)
C(11)–C(12)	1.408	1.408	1.381(5)
C(12)–C(7)	1.416	1.409	1.382(4)
C(4)–C(13)	1.420	1.418	1.465(3)
C(13)–C(14)	1.416	1.416	1.394(4)
C(14)–C(15)	1.408	1.418	1.384(4)
C(15)–C(16)	1.410	1.410	1.387(4)
C(16)–C(17)	1.411	1.407	1.390(3)
C(17)–C(18)	1.411	1.404	1.380(3)
C(18)–C(13)	1.415	1.416	1.398(3)
ϕ	-96.0	-117.7	-123.3
ψ	-154.0	-156.5	-159.8
ω	-78.9	-83.5	-76.2

* In space group $P4_12_12$.

using a laboratory X-ray powder diffraction pattern. Coupled with the knowledge of the cell parameters based on powder pattern indexing, the molecular packing analysis method successfully located the rofecoxib structures as the energetically most favorable solutions among the common tetragonal space groups. The force field “Dreiding 2.21” proved to be suitable for the rofecoxib system in which only van der Waals interactions were present between molecules. The direct space method structure solutions were evaluated by packing energy calculation. The correct rofecoxib crystal structures were obtained by direct space method using a molecular model with standard S–C and S=O bond distances. The bond distances of the S–C and S=O bonds proved to be important in order to locate the correct conformation of the methylsulfonyl group. We found that molecular packing analysis method and direct space method can be powerful alternatives to the

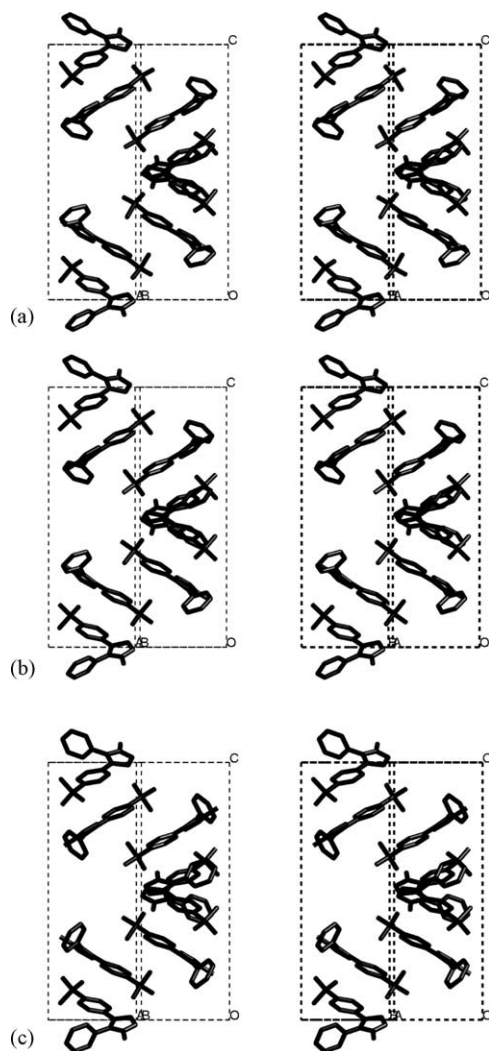


Fig. 8. View down the (110) direction of the rofecoxib crystal structures obtained from (a) single crystal, (b) molecular packing analysis calculation, and (c) direct space method.

single crystal method when used together and carefully.

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