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Solid-state ^{13}C NMR study of indomethacin polymorphism

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Abstract

The purpose of this study was to analyze the difference in the molecular conformation packed in the crystal lattice between the meta-stable α-form and stable γ-form of indomethacin on the basis of solid-state ^{13}C NMR spectral patterns. The chemical shifts of each resonance of the α-form were distinctly different from the γ-form. Each carbon nucleus of the γ-form showed a single signal with no splitting. In contrast, carbon nuclei of the α-form showed a complicated set of resonances for each carbon. For some carbons of the α-form, four signals assigned to one carbon were observed at 203 K. Two of these four signals were merged between the temperature range from 203 to 343 K without a transformation in the crystal structure. It was found that solid-state ^{13}C NMR can be a powerful tool to estimate the number of molecular conformations as well as configurational differences in the packing of molecules in a unit cell.

Keywords: Solid-state ^{13}C NMR; Indomethacin; Polymorphism

1. Introduction

Pharmaceutical products and active pharmaceutical ingredients are mainly solid, and many pharmaceutical solids can exist in more than one solid form, as is often the case in polymorph, amorphous, solvate, and co-crystal substances. The differences in the solid pharmaceutical forms result in different physical and chemical properties and occasionally affect color, bioavailability, dissolution rate, stability, manufacturability, etc. Therefore, the characterization of pharmaceutical solid forms is very important to ensure the supply of pharmaceuticals of standard quality (Haleblian and McCrone, 1969; Bryn et al., 1995; Byrn et al., 1999; Gibson, 2001; Vippagunta et al., 2001; Raw et al., 2004; Rodriguez-Spong et al., 2004). There have been many studies on the physicochemical characterization of solid pharmaceuticals using such techniques as microscopy, X-ray analysis, thermal analysis, spectroscopy, dynamic vapor sorption, and others. These studies were summarized by Byrn et al. (1999), Bugay (2001), and Stephenson et al. (2001).

Polymorphs are defined as different arrangements and/or conformations of the molecules within the crystal lattice. Elucidating the arrangement and/or conformation of molecules is often crucial to understanding the solid-state chemistry of a drug. In general, single-crystal X-ray analysis is helpful in understanding the crystal packing of individual molecules within the crystal lattice. However, X-ray crystallographic analysis is not always

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applicable, for example, when no single crystal of sufficient size (usually greater than 0.01 mm in length) can be obtained as a meta-stable form.

Solid-state nuclear magnetic resonance (NMR) is also a powerful tool for understanding solid-state chemistry. It can provide information on variations in hydrogen bond networks, molecular conformation, and molecular mobility (Bugay, 2001). Therefore, several studies used solid-state NMR to characterize pharmaceutical solids. Those were reviewed and discussed in detail, along with other spectroscopic techniques, in Byrn et al. (1999) and Bugay (2001).

Indomethacin ([1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-yl] acetic acid) is an antipyretic and antiinflammatory drug used in many pharmaceutical preparations (Shen et al., 1963; Winter et al., 1963). The polymorphic forms of indomethacin have been extensively investigated (Yamamoto, 1968; Borka, 1974; Spychala et al., 1977; Kaneniwa et al., 1985; Lin, 1992; Adronis and Zografi, 2000; Slavin et al., 2002; Watanabe et al., 2002). The crystal structures of indomethacin have been determined using X-ray crystallographic analysis; Kistenmacher and Marsh (1972) determined the structure of the stable γ-form and Chen et al. (2002) determined that of the meta-stable α-form. There have also been reports on the relationship between the polymorphs of indomethacin and biological absorption rate. Since the dissolution rate of the meta-stable form is more rapid than that of the stable form, the biological absorption rate of the meta-stable form is also greater than that of stable form. It has been reported that the rectal absorption rate of the meta-stable α-form in the rat was greater than the stable γ-form (Yokoyama et al., 1979).

Solid-state ^{13}C NMR spectra yield information on hydrogen bond networks and molecular conformations in crystal structures. Although the polymorphs of indomethacin were investigated using solid-state ^{13}C NMR by Lin (1992), the results of that study showed only that each polymorph has a different NMR spectral pattern. The reasons for the difference in the solid-state ^{13}C NMR spectral pattern of each polymorph thus remain unresolved.

The purpose of this study was to analyze the difference in the molecular conformation packed in the crystal lattice between the α-form and γ-form on the basis of solid-state ^{13}C NMR spectral patterns. In addition, the temperature dependence of solid-state ^{13}C NMR spectra for each polymorph was examined.

2. Materials and methods

2.1. Materials

The γ-form (Sigma I-8280, UPS-std, lot no. 61K13681) was purchased from Sigma Chemical (St. Louis, MO, USA). The α-form was obtained by recrystallization. Briefly, a solution of indomethacin 2 g (Sigma I-8280, UPS-std, lot no. 61K13681) in ethanol 7 mL at 70 °C was rapidly cooled to 4 °C. Then the solution was stored at 4 °C overnight. The precipitated α-form crystals were collected by filtration and dried in vacuo at 40 °C.

2.2. Methods

2.2.1. X-ray powder diffraction

X-ray powder diffraction (XRPD) patterns were obtained using a Rigaku (Tokyo, Japan) RINT2200 powder diffraction system, equipped with an Ultima$^+$ (Tokyo, Japan) goniometer I-type in $\theta/2\theta$ geometry. The X-ray generator was operated at 40 kV and 40 mA, using Cu Kα radiation. For the α-form, the scans were performed in the range between 2° and 40° with a scan rate of 0.25°/min and step size of 0.01° at room temperature. For the γ-form, the scans were performed between 2° and 40° with a scan rate of 1°/min and step size of 0.02° at room temperature. For both the α-form and γ-form, the slits used were: 0.5° (DS), 0.3 mm (RS), and 0.5° (SS).

2.2.2. Solid-state NMR

2.2.2.1. Comparison of solid-state ^{13}C NMR spectral patterns. Solid-state ^{13}C NMR spectra were obtained using a Chemagnetics (Fort Collins, CO, USA) CMX-400 instrument operating at a carbon frequency of 100.6 MHz. Each sample was spun at the magic angle (54.7°) at a frequency of 15 kHz at ambient temperature using a probehead with an internal diameter of 4 mm. The spectra were obtained using the cross polarization magic angle-spinning (CP/MAS) methods. The contact time was 5 ms, and the pulse delay between scans was 30 s.

The quantitative solid-state ^{13}C NMR spectra were obtained using the dipole decoupling magic angle spinning (DD/MAS) method. The pulse delay between scans was 10 s. This value is five-fold greater than the T1 value for signals of methyl carbons. Therefore, it was possible to estimate the signal intensities quantitatively. The chemical shifts of the entire spectra were measured using the methylene signal of adamantane at 38.52 ppm at 298 K as an external reference.

2.2.2.2. Temperature dependence of solid-state ^{13}C NMR spectral patterns. Solid-state ^{13}C NMR spectra were obtained using a Bruker (Karlsruhe, Germany) AV300WB instrument operating at a carbon frequency of 75.48 MHz. Each sample was spun at the magic angle (54.7°), at the frequency of 4, 4, and 3 kHz, at 343, 298, and 203 K, respectively, using a probehead with an internal diameter of 7 mm. All spectra were obtained using a combination of the CP/MAS and the total sideband suppression (TOSS) methods. The contact time was 1 ms, and the pulse delay between scans was 3 s. The chemical shifts were measured using the carbonyl carbon signal of glycine at 176.03 ppm at 298 K as an external reference.

2.2.3. Solution-phase NMR

All solution-phase NMR spectra were obtained using a Bruker DRX-500 instrument operating at a proton frequency of 500.13 MHz and a carbon frequency of 125.77 MHz, equipped with a 5-mm broadband probehead at 300 K. Indomethacin was dissolved in deuterium methanol at a final concentration of approximately 20 mg/mL and pipetted into a 5-mm outer diameter NMR sample tube containing approximately 0.5 mL. The chemical shifts were adjusted using the solvent signal at 3.31 ppm for ^{1}H NMR spectra and that at 49.2 ppm for ^{13}C NMR

spectra. Each ^{1}H NMR spectrum was recorded with a data size of 32 K and a spectral width of 20 ppm (digital resolution per point 0.32 Hz). Each ^{13}C NMR spectrum was recorded with a data size of 32 K and a spectral width of 250 ppm (digital resolution per 1 Hz). Heteronuclear multiple-quantum coherence (HMQC) and heteronuclear multiple-bond connectivity (HMBC) spectra were recorded with an F2 size of 2 K and an F1 size of 128 W when free induction decays (FIDs) were collected, and only the F1 direction was zerofilled to 1 K when they were transformed.

2.2.4. Crystal packing drawing

Crystal packing drawings of the α-form and γ-form were depicted using Material Studio ver. 2.2 (Accerlys Inc., San Diego, CA, USA), based on the Cambridge Crystallographic Data Center (CCDC) deposition number 201766 and the Cambridge Structural Database (CSD) reference code INDMET for the α-form and γ-form, respectively.

3. Results and discussion

3.1. Comparison of solid-state ^{13}C NMR spectral patterns

The XRPD patterns for both the α-form and γ-form are shown in Fig. 1. The patterns were in good agreement with previously published diffraction data (Yamamoto, 1968), and both our data and published data showed identical characteristic peaks, for example, for the α-form at 8.4°, 11.9°, 14.4°, 18.0°, and 22.1° (2θ), and for the γ-form at 11.6°, 19.6°, 21.9°, 26.6°, and 29.4° (2θ). Furthermore, the 2θ values of the data coincided well with those of the calculated XRPD pattern based on single-crystal structural data (Fig. 1), and thus the crystals obtained were regarded as pure crystal forms.

The molecular packing of the γ-form is shown in Fig. 2. It was previously determined that the space group is P1 (triclinic) with $Z = 2$, indicating that one pair of molecules is packed in the asymmetric unit (Kistenmacher and Marsh, 1972). On the other hand, the crystal structure of the α-form has recently been analyzed by Chen et al. (2002), who found that the space group is $P2_1$ (monoclinic) with $Z = 6$, indicating that set of three molecules are packed in the asymmetric unit (Fig. 3).

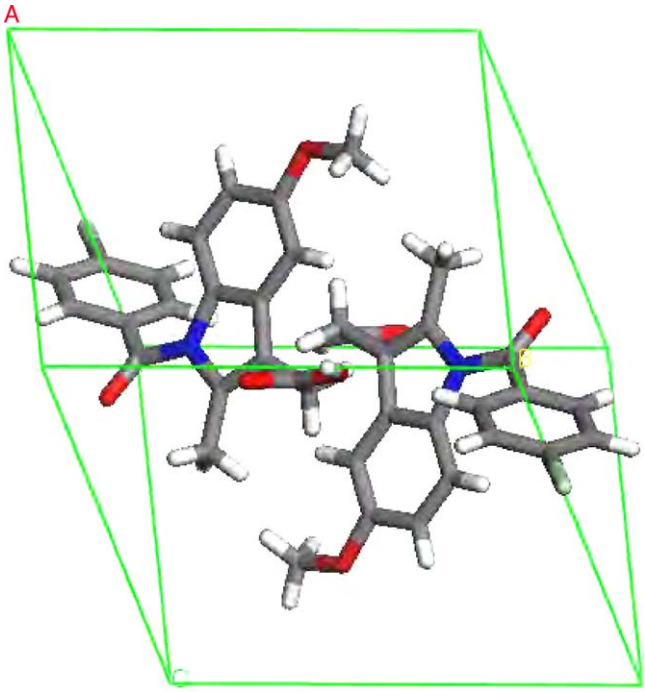

Fig. 2. Crystal structure of the γ-form. Single-crystal data were from the Cambridge Structural Database (CSD) reference code INDMET.

The solid-state ^{13}C CP/MAS NMR spectra for the α-form and γ-form are shown in Fig. 4. The spectrum of the γ-form shows a single resonance signal without splitting, while the spectrum of the α-form shows signals with splitting. Based on the results of crystal structural analysis, the γ-form has one conformation molecule in the unit cell, while the α-form has three conformation molecules in the unit cell. For the solid-state ^{13}C CP/MAS NMR spectra of the α-form, therefore, signals with splitting could be explained by three types of conformationally different molecules packed in the unit cell.

The solid-state NMR spectra were assigned by based on the solution-phase NMR assignments in ^{1}H NMR, ^{13}C NMR, HMQC, and HMBC spectra. Based on Fig. 4, for the solid-state NMR spectrum of the α-form, carbon numbers 5, 12, and 13 apparently consisted of three signals each, while the numbers

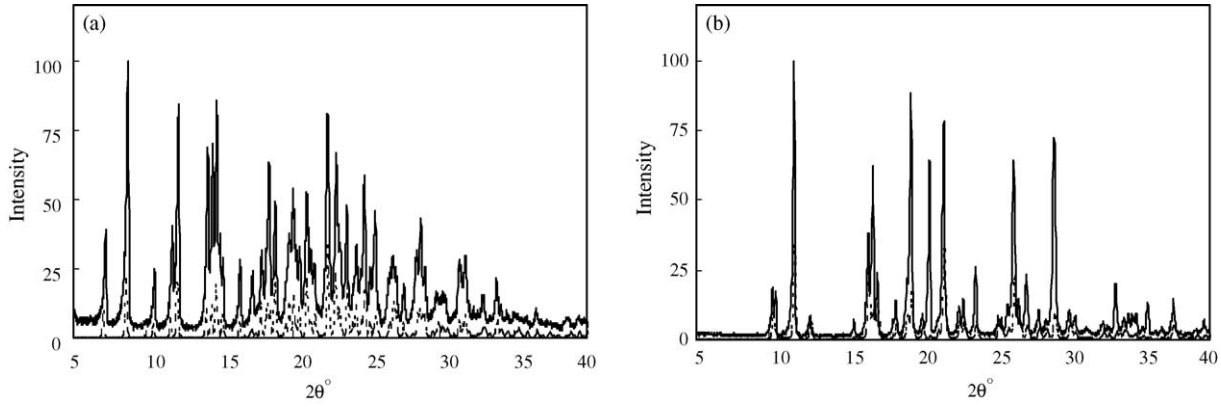

Fig. 1. Comparison of X-ray diffraction patterns calculated from single-crystal data (dashed line) and experimental data (solid line). (a) α-Form; (b) γ-form. Single-crystal data were from the Cambridge Crystallographic Database Center (CCDC) deposition number 201766 and the Cambridge Structural Database (CSD) reference code INDMET, for the α-form and γ-form, respectively.

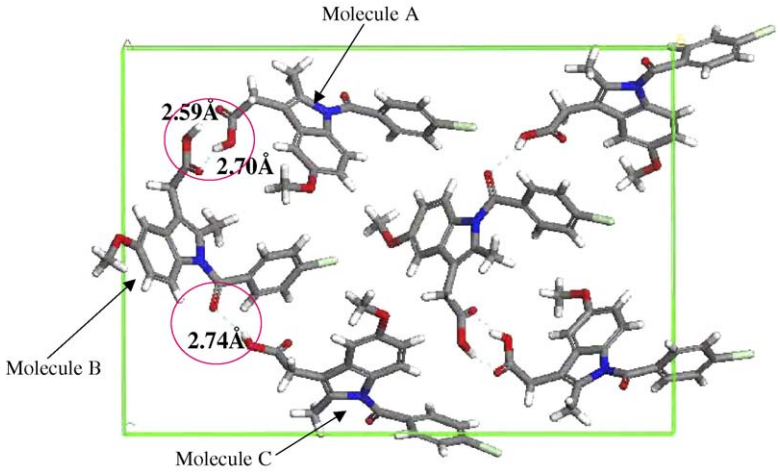

Fig. 3. Crystal structure of the α-form showing hydrogen bonding (in circled areas) and length. Single-crystal data were from the Cambridge Crystallographic Database Center (CCDC) deposition number 201766.

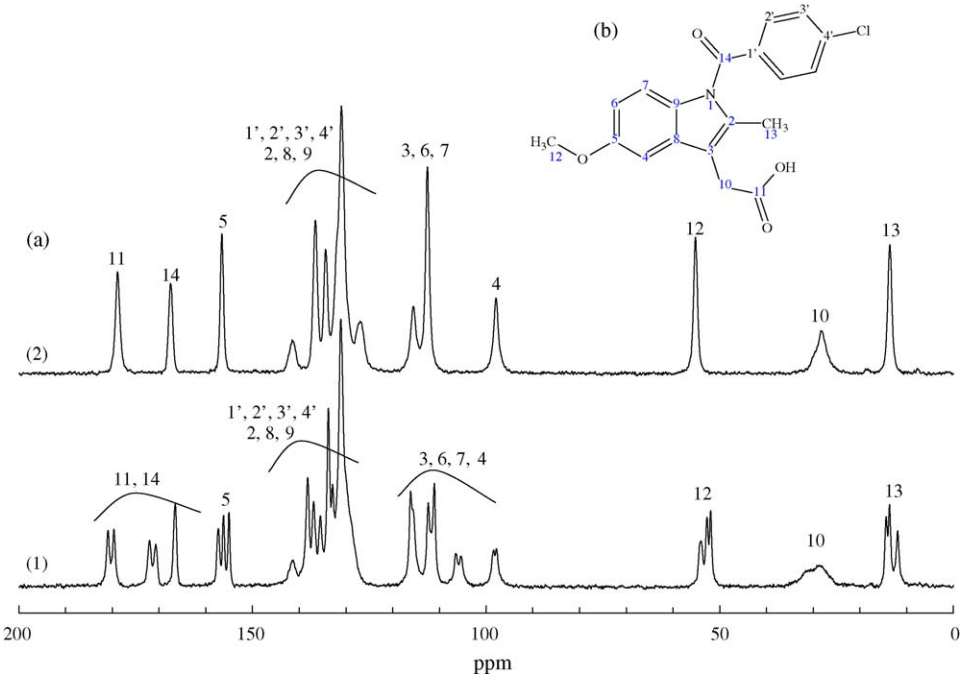

Fig. 4. (a) Solid-state ^{13}C CP/MAS NMR spectra of crystal forms. 1, α-form; 2, γ-form. (b) Structure of indomethacin with atoms numbered.

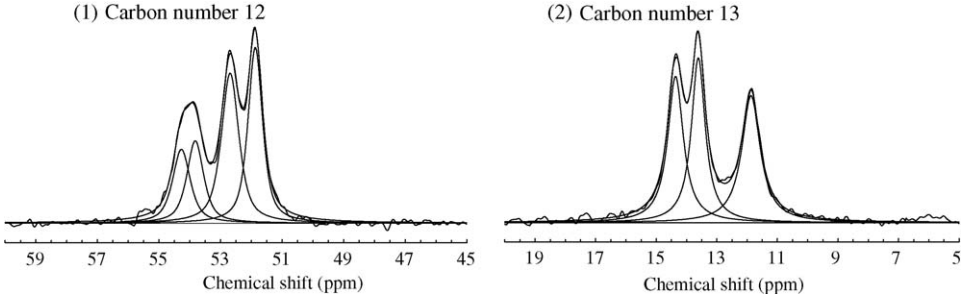

Fig. 5. Methyl carbon signals in solid-state ^{13}C DD/MAS NMR spectra of the α-form using curve-fitting analysis. Assigned carbon numbers refer to the structure in Fig. 4(b).

Table 1
Curve-fitting parameter of the 13C DD/MAS NMR spectra for methyl carbon regions of the α-form

Carbon no.	Parameter	Component		
		1	2	3
13	Height	0.76	0.86	0.66
	Width (Hz)	31.2	28.2	37.2
	Chemical shift (ppm)	14.36	13.61	11.87
	Lorentzian/Gaussian	1/0	1/0	1/0
	Area (%)	33.0	33.2	33.8

Carbon no.	Parameter	Component			
		1	1′	2	3
12	Height	0.38	0.42	0.77	0.90
	Width (Hz)	34.2	32.2	34.2	28.2
	Chemical shift (ppm)	54.27	53.82	52.69	51.87
	Lorentzian/Gaussian	0.7/0.3	0.7/0.3	0.7/0.3	0.7/0.3
	Area (%)	16.6	17.6	33.4	32.6

All chemical shifts of the respective carbon atoms refer to the structure in Fig. 4(b).

for other signals were complicated. Unfortunately, the signals in the regions of 98–117 ppm, 130–141 ppm, and 167–181 ppm in the α-form spectrum still cannot be assigned in detail. When the NMR signal of the α-form was analyzed in detail, signals at 52–54 ppm assigned to carbon number 12 consisted of two sharp signals and one broad one. Similarly, signals at 155–158 ppm assigned to carbon number 5 also showed the same patterns. The regions of 5–20 ppm and 45–60 ppm in the solid-state ^{13}C DD/MAS NMR spectra of the α-form are shown in Fig. 5, because this measurement method focused on the quantity of methyl carbons determined. The two-methyl regions of the spectrum were deconvoluted using the nonlinear least-squares method. Lorentzian and Lorentzian/Gaussian (the ratio of Lorentzian is 0.7) lineshapes were applied to carbon numbers 13 and 12, respectively. Fig. 5 shows the methyl carbon regions for carbon numbers 13 and 12 obtained from curve-fitting analysis. Table 1 lists the details of the curve-fitting results, which show that deconvolution is a subroutine that can adjust the parameters of a set of lines to fit peaks in an actual spectrum. Thus, the α-form has four and three signals for each methyl carbon, with intensity ratios of 1:1:2:2 and 2:2:2 for methyl carbons 12 and 13, respectively. This indicates that carbon number 12 could exist in four different types of magnetic environment, i.e., four different conformational molecules are present in the unit cell, while three different conformational molecules are present in carbon number 13.

These observations represent new information on the number of molecules in the asymmetric unit of the α-form. Based on the results of single-crystal X-ray crystallographic analysis, there are three molecules, each with a different conformation, in the asymmetric unit, which were designated molecules A, B, and C (Fig. 3). Table 2 shows the equivalent isotropic displacement parameters (U_{ep}) of the α-form which were taken from CCDC deposition no. 201766. For 14 carbons (74%) among the total carbons of the α-form with the same carbon number, U_{ep} values of molecule A are greater than those of molecule B and molecule C. For example, the U_{ep} values of carbon number 5 of molecules A, B, and C are 0.0375, 0.0322, and 0.0302 Å, respectively; the U_{ep} values of carbon nunber 12 of molecules A, B, and C are 0.0540, 0.0410, and 0.0393 Å, respectively; and the U_{ep} values of carbon nunber 13 of molecules A, B, and C are 0.0460, 0.0364, and 0.0410 Å, respectively.

Table 2
Equivalent isotropic displacement parameters of molecules A, B, and C of the α-form

Carbon no.	Molecule A	Molecule B	Molecule C
13	0.0460	0.0364	0.0410
10	0.0421	0.0331	0.0316
12	0.0540	0.0411	0.0393
4	0.0367	0.0276	0.0306
6	0.0396	0.0333	0.0319
3	0.0342	0.0289	0.0292
7	0.0340	0.0335	0.0329
3′	0.0386	0.0417	0.0392
	0.0359	0.0390	0.0406
2′	0.0398	0.0357	0.0347
	0.0344	0.0375	0.0377
8	0.0313	0.0280	0.0272
9	0.0308	0.0273	0.0283
1′	0.0325	0.0296	0.0335
2	0.0335	0.0294	0.0335
4′	0.0331	0.0377	0.0370
5	0.0375	0.0322	0.0302
14	0.0349	0.0313	0.0347
11	0.0404	0.0341	0.0317

All chemical shifts of the respective carbon atoms refer to the structure in Fig. 4(b). Unit: angstrom (Å). Average: 0.0350; standard deviation: 0.0050.

Because the molecules mutually form a hydrogen-bonded carboxylic acid dimer between carbon number 11 of molecule A and molecule B, and hydrogen bonding occurs between the carboxylic acid group of molecule C (carbon number 11) and the amide carbonyl group of molecule B (carbon number 14), the U_{ep} values of carbon number 11 of molecules B and C, and carbon number 14 of molecule B are relatively small at 0.0341, 0.0317, and 0.0313 Å, respectively, while the average and the standard deviation of all of U_{ep} values are 0.0350 and 0.0050 Å, respectively. Carbon number 12 of molecule A could have the greatest vibration in comparison with the other carbons, because the U_{ep} value of carbon number 12 of molecule A has the highest value (Table 2). Presumably, molecule A swings due to the vibration of carbon number 12 of molecule A. Carbon number 5 of molecule A might be the most affected by this movement of carbon number 12, because these two carbons are neighbors.

As a result, carbon number 12 of the methoxyl group of molecule A appears to be present in two sites. It is concluded that the reason why complicated signal patterns are observed in the solid-state ^{13}C NMR spectrum of the α-form of indomethacin is that it is composed of three different conformational molecules (A, B, and C) and moreover, the methoxyl group (carbon number 12) and quaternary carbon connected to the methoxyl group (carbon number 5) of molecule A are present in two sites at room temperature. Solid-state ^{13}C NMR can thus estimate the

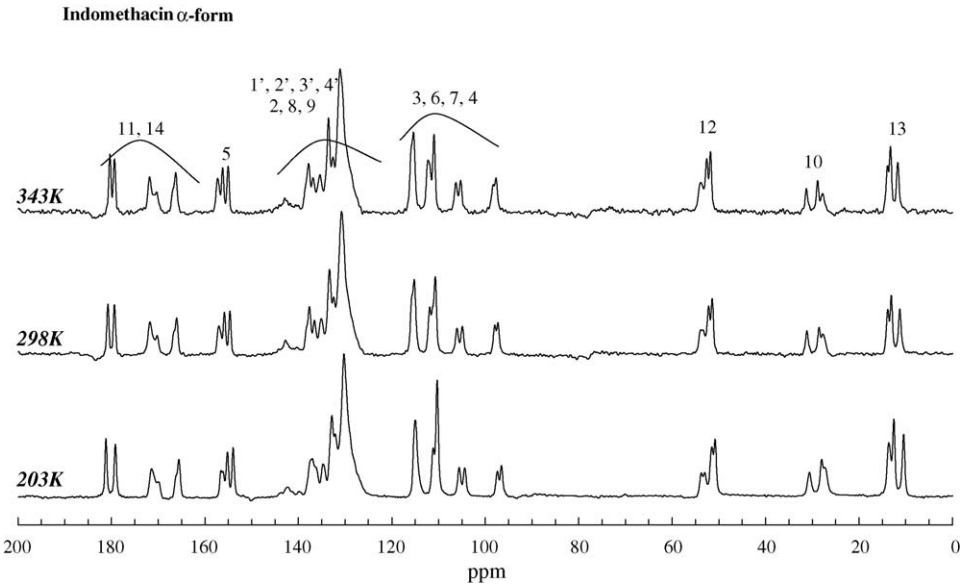

Fig. 6. Solid-state ^{13}C CP/MAS TOSS NMR spectra of the α-form at various temperatures. Assigned carbon numbers refer to the structure in Fig. 4(b).

number of molecular conformations as well as configurational differences in a portion of the molecule.

3.2. Temperature dependence of solid-state ^{13}C NMR spectral patterns

The temperature dependence of solid-state ^{13}C CP/MAS TOSS NMR spectra of the α-form and γ-form are shown in Figs. 6 and 7, respectively. As seen in Figs. 6 and 7, all of the solid-state ^{13}C NMR spectra of the α-form and γ-form exhibited almost the same spectral pattern in the temperature range from 203 to 343 K, indicating that they do not change their crystal structures over this temperature range.

However, when investigating the carbon numbers 13, 10, 12, and 5 regions of the α-form, which are at 12–15 ppm, 29–32 ppm, 52–54 ppm, and 155–158 ppm, the solid-state NMR spectrum of the α-form of indomethacin exhibits temperature dependence in the range from 203 to 343 K (Fig. 6). Although it is not clear from the one-dimensional NMR data alone why the chemical shifts of some carbons moved down field with an increase in the measurement temperature, we assume that the shift change is related to the movement of the side chain. The shift changes of the other frame carbons, on the other hand, were not great compared with those of the side chains. We therefore assume that the down field shifts of positions 5, 12, and 13 result from the

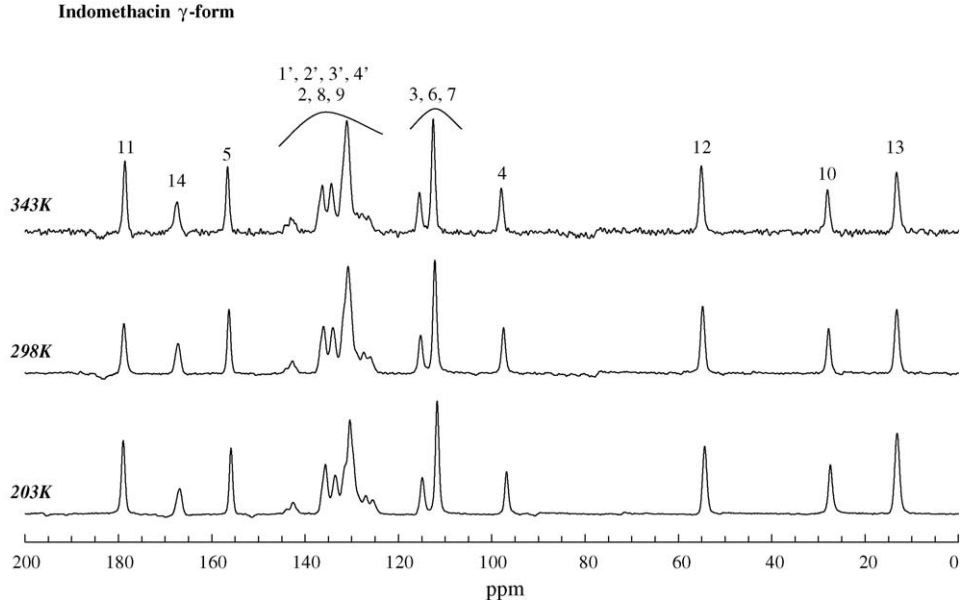

Fig. 7. Solid-state ^{13}C CP/MAS TOSS NMR spectra of the γ-form at various temperatures. Assigned carbon numbers refer to the structure in Fig. 4(b).

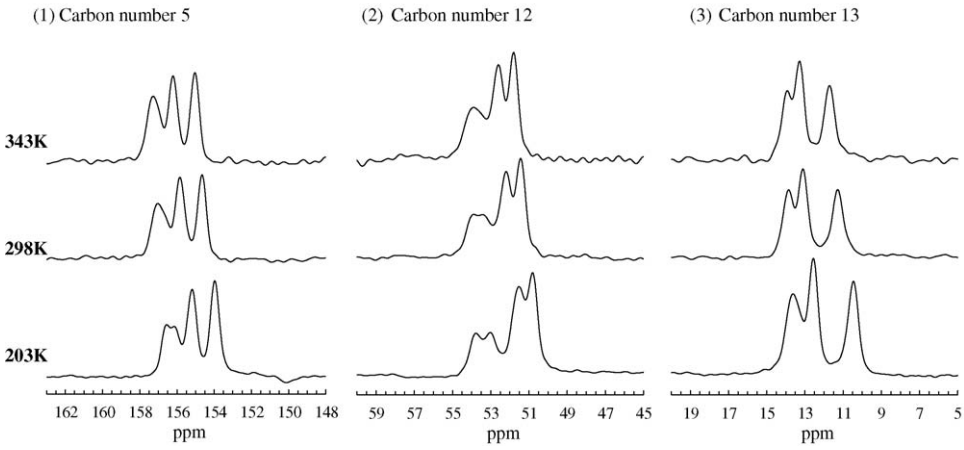

Fig. 8. Solid-state ^{13}C CP/MAS TOSS NMR spectra of the α-form at various temperatures with expansion of the plot of the regions of carbon numbers 5, 12, and 13. Assigned carbon numbers refer to the structure in Fig. 4(b).

segmental movement of the side chain(s) at higher temperature.

In addition, with the segmental movement of the side chain(s) of carbon number 12 (methoxyl group) at higher temperature, the highest frequency signals (53–54 ppm) clearly moved toward conflation as the temperature increased to 343 K. Carbon number 5 (quaternary carbon connected to the methoxyl group) also showed the same temperature dependence. The chemical shift data of carbons 5, 12, and 13 of the α-form in the solid-state ^{13}C CP/MAS TOSS NMR spectra, along with their temperature dependence, are shown in Fig. 8. Thus, for molecule A, one of the three types of molecular conformation of the α-form, two sites of conformation were observed at 203 K, and at higher temperature, the two sites of conformation merged by the averaging of the chemical and physical environmental conditions without changing the crystal structure.

4. Conclusion

The solid-state NMR spectra patterns of the α-form are clearly different from those of the γ-form. Each carbon of the γ-form shows a single signal without splitting. In contrast, those of the α-form show a complicated set of signals for each carbon. For some carbons of the α-form, four signals assigned to one carbon were observed at 203 K. The chemical shift of two of those signals changed in the temperature range from 203 to 343 K. This means that a slight conformational change was occurred on a portion of the molecule in this temperature range. Those two signals merged as temperature increased without changing the crystal structure. It was found that solid-state ^{13}C NMR can be a powerful tool to estimate the number of molecular conformations as well as configurational differences in the packing of molecules in a unit cell.

Acknowledgments

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