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# Physicochemical and Crystal Structure Analyses of the Antidiabetic Agent Troglitazone

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**The antidiabetic agent troglitazone has two asymmetric carbons located at the chroman ring and the thiazolidine ring and is produced as a mixture of equal amounts of four optical isomers, 2*R*-5*S*, 2*S*-5*R*, 2*R*-5*R*, and 2*S*-5*S*. The crystalline powdered drug substance consists of two diastereomer pairs, 2*R*-5*R*/2*S*-5*S* and 2*R*-5*S*/2*S*-5*R*. There are many types of crystals obtained from various crystallization conditions. The X-ray structure analysis and the physicochemical analyses of troglitazone were performed. The solvated crystals of the 2*R*-5*R*/2*S*-5*S* pair were crystallized from several solutions: methanol, ethanol, acetonitrile, and dichloromethane. The ratio of solvent and troglitazone was 1 : 2 (L1/2-form). The monohydrate crystals were obtained from aqueous acetone solution (L1-form). On the other hand, only an anhydrate crystal of the 2*R*-5*S*/2*S*-5*R* pair was crystallized from various solutions (H0-form). The dihydrous mixed crystal (MA2-form) was obtained from a mixture of the two diastereomer pairs of 2*R*-5*R*/2*S*-5*S* and 2*R*-5*S*/2*S*-5*R* in equal amounts by the slow evaporation of aqueous acetone solution. The crystal structure of the MA2-form is similar to the H0-form. When the MA2 crystal was kept under low humidity, it was converted into the dehydrated form (MA0-form) with retention of the single crystal form. The structure of the MA0-form is isomorphous to the H0-form. The MA2-form was converted into the MA0-form and *vice versa* with retention of the single crystal under low and high humidity, respectively. The crystallization and storage conditions of the drug substances were successfully analyzed.**

**Key words** hydrate; dehydration; mixed crystal; antidiabetic agent; crystal transformation; single crystal structure X-ray analysis

The fundamental physicochemical properties of drug substances depend on their characteristics in the solid.[1—3] The drug substances sometimes crystallize in the polymorphic form or in the hydrate or solvate form, and furthermore become amorphous depending on the manufacturing process of the crystallization, drying, compression, and storage.[4—9] Different crystal forms should have different lattice energy since they generally have different noncovalent molecular interactions in their crystal packing, such as hydrogen bonding, electrostatic, $\pi$–$\pi$ stacking, and van der Waals interactions, which are due to different molecular conformation and crystal packing depending on a variety of characteristics in the solid state.[10] Therefore it is very important in the development of drug substances to select the best solid form from a variety of solid substances and to establish the crystallization method that will give crystals with constant physical properties.

Troglitazone, (±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-dioxothiazolidine (Fig. 1), is an oral antidiabetic agent that has effective insulin-resistant diabetic activity[11] and significant lipid peroxide–lowering activity.[12] Troglitazone has two asymmetric carbons located at the C-2 position of the chroman ring and the C-5 position of the thiazolidine ring. The bulk drug substance therefore consists of four stereoisomers, 2*R*-5*S*, 2*S*-5*R*, 2*R*-5*R*, and 2*S*-5*S* with equal composition. The diasteromeric pairs are called the H-pair and L-pair, respectively, since the 2*R*-5*S*/2*S*-5*R* pair has a higher melting point than the 2*R*-5*R*/2*S*-5*S* pair.[13] The cooling crystallization method reproducibly gives a mixture of the crystalline diastereomeric pairs, H-pair and L-pair, with constant thermal properties.[13] Moreover, the dihydrous mixed crystal (MA2-form) composed of the H-pair and L-pairs[14] was obtained. In this paper, the physicochemical properties of the H-pair and L-pair crystals, and the mixed crystal (MA-form) are discussed using single crystal X-ray analysis, powder X-ray diffractometry, differential scanning calorimetry (DSC), Karl Fischer moisture titration, and elemental analysis. Finally, an interesting phase transformation from the MA2-form into the dehydrated mixed crystal MA0-form, which has a similar cell constant to the H-pair compound (H0-form) is reported.

## Experimental

**Preparation of Different Crystal Forms** Anhydrate Crystal of H-Pair (H0-Form): The H0-form crystals were obtained from an aqueous acetone

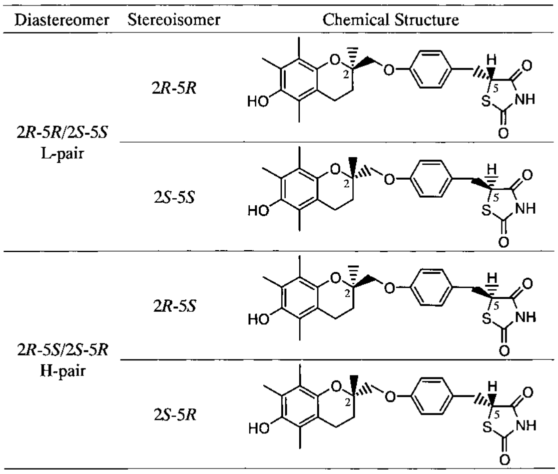

Fig. 1. Chemical Structure of Troglitazone

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solution by slow evaporation at room temperature.

Monohydrate Crystal of L-Pair (L1-Form): The L1-form crystals were recrystallized from an aqueous acetone solution by slow evaporation at room temperature and were stored under relative humidity (RH) of 60% at 25 °C.

Hemisolvate Crystals of L-Pair (L1/2-Form): The L1/2-form crystals were obtained from an anhydrous solution, methanol, ethanol, acetonitrile, or dichloromethane, by slow evaporation at room temperature.

Dihydrous Mixed Crystals (MA2-Form): The MA2-form crystals were obtained from an aqueous acetone solution of the mixture of the H- and L-pair compounds by slow evaporation at room temperature.

Dehydrated Mixed Crystals (MA0-Form): The MA0-form crystals were prepared by storing the MA2-form crystals below 30% RH at room temperature for several days.

**Analytical Methods. Powder X-Ray Diffraction** Powdered sample was packed into a holder and the diffraction peaks were obtained on a model Rint 2200 diffractometer (Rigaku Denki Co. Ltd.) with graphite-monochromated Cu-$K\alpha$ radiation (40 kV, 40 mA). The $2\theta$ range was 3 to 40°, and the scan step and scan rate were 0.02° and 1 or 4°/min, respectively.

**DSC** DSC curves were recorded on a model DSC3100 instrument (Mac Science Co. Ltd.). Approximately 3 mg of each sample in an open pan was heated from 0 to 230 °C at 5 or 10 °C/min under nitrogen gas (flow rate 100 ml/min).

**Water Content Titration** The water content was determined by the Karl Fischer method (model MKA-210, Kyoto Denshi Kogyo Co. Ltd.). Samples (100—300 mg) were accurately weighed and quickly transferred to the titration vessel containing anhydrous methanol prior to titration. Then the solutions were titrated using the Karl Fischer reagent SS® (Mitsubishi Chemical Co. Ltd., Japan).

**Single Crystal X-Ray Structure Analyses of MA2-Form, MA0-Form, and H0-Form** The X-ray diffraction measurements were carried out at $-50$ °C on a Rigaku R-AXIS RAPID using graphite-monochromated Mo$K\alpha$ radiation. Unit cell parameters were obtained from least-squares refinement of the setting angles of the number of reflections from the data collection. The structures were solved using the direct methods program SIR97,[15] and full-matrix least-squares refinement on $F^2$ was completed using the program SHELXL 97.[16] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in the difference Fourier map to the extent possible. The positions of the other hydrogen atoms were calculated geometrically. All hydrogen atoms were refined isotropically.

**X-Ray Structure Determination of L1/2-Form** X-Ray intensity data were collected using a four-circle diffractometer (Mac Science MXC-18) with graphite-monochromated Cu and Mo$K\alpha$ radiation. The $\omega$–$2\theta$ scan mode was used. The intensity data of the L1/2-forms were recorded at room temperature. Each unit cell dimension was refined using 24 reflections. The intensities were corrected for absorption on the basis of a $\Psi$-scan. The structures were solved using the direct method program SIR92.[17] Refinements were performed with the CRYSTAN (Mac Science) Ver. 6.3.3. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located in the difference Fourier map and were refined isotropically.

## Results and Discussion

**Preparation of Different Modifications of the L-Pair and H-Pair Compounds** For the L-pair, five types of crystals were obtained from solutions of methanol, ethanol, acetonitrile, dichloromethane, and aqueous acetone. The elemental analysis and percent water content for each crystal are summarized in Table 1. The values indicated that the four crystals obtained from methanol, ethanol, acetonitrile, and dichloromethane solvents have one solvent molecule per two troglitazone molecules and that the crystal from an aqueous acetone solution has one water molecule per one troglitazone molecule. The L-pair formed four solvate crystals (L1/2-form) and one monohydrate crystal (L1-form). The small difference may be attributed to slight solvent loss during the drying process. The powder X-ray diffraction profiles were similar to each other, as shown in Fig. 2, although a slight

Table 1. Stoichiometric Analysis Based on Solvent Mass of the L-Pair Compound (Elemental Analysis, Water Content)

| Crystal form | Crystallization solvent chemical form | | Elemental analysis (%) | | | | | Water content (%) |
|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | S | Cl | |
| L1/2-form | MeCN | Found | 64.56 | 5.96 | 4.42 | 6.72 | — | — |
| | 1/2 MeCN solvate | Calcd | 64.81 | 6.23 | 4.43 | 6.94 | — | — |
| L1/2-form | MeOH | Found | 63.83 | 6.25 | 3.05 | 7.06 | — | — |
| | 1/2 MeOH solvate | Calcd | 64.15 | 6.39 | 3.06 | 7.00 | — | — |
| L1/2-form | EtOH | Found | 64.20 | 6.35 | 3.00 | 7.08 | — | — |
| | 1/2 EtOH solvate | Calcd | 64.54 | 6.50 | 3.02 | 6.90 | — | — |
| L1/2-form | $CH_2Cl_2$ | Found | 61.06 | 5.94 | 2.92 | 6.73 | 6.53 | — |
| | 1/2 $CH_2Cl_2$ solvate | Calcd | 61.14 | 5.93 | 2.92 | 6.69 | 6.02 | — |
| L1-form | Acetone–$H_2O$ | Found | 63.12 | 6.13 | 3.05 | 7.10 | — | 3.5 |
| | Monohydrate | Calcd | 62.73 | 6.36 | 3.05 | 6.98 | — | 3.9 |

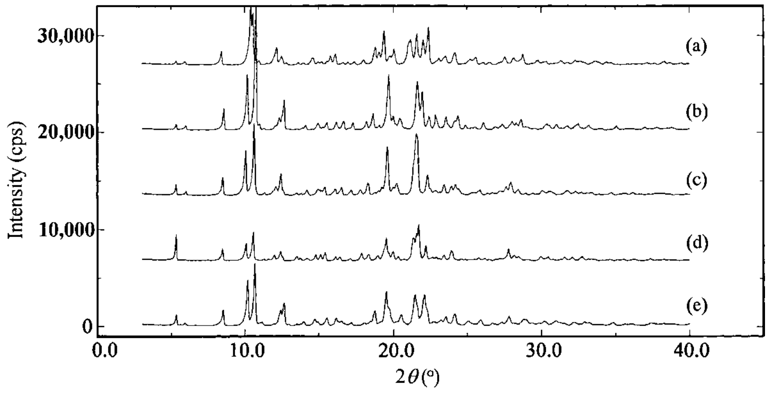

Fig. 2. Powder X-Ray Diffraction Patterns of the Solvate and Hydrate of the L-Pair Compound

L1/2-form: (a) acetonitrilate; (b) methanolate; (c) ethanolate; (d) dichloromethanoate; L1-form: (e) monohydrate.

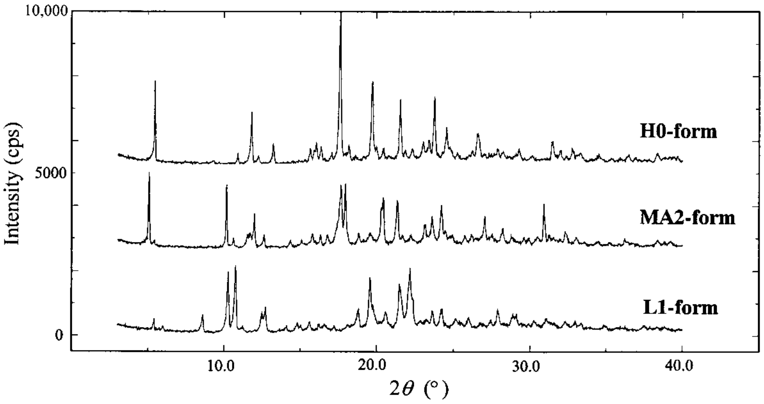

Fig. 3. Powder X-Ray Diffraction Patterns of Three Crystal Forms of Troglitazone

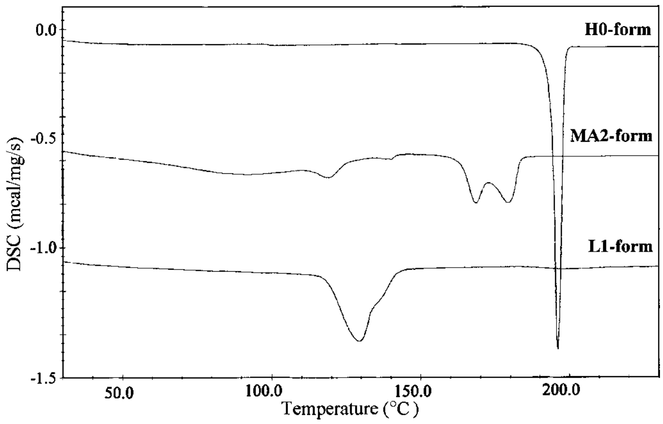

Fig. 4. DSC Curves of Three Crystal Forms of Troglitazone

difference was seen in the ranges of $2\pi$=8—12° and 18—23°. This suggests that all the L-pair crystals are isomorphous.

The H-pair was also crystallized from various solutions of methanol, ethanol, acetonitrile, dichloromethane, acetone, and aqueous acetone. However, the crystals thus obtained had the same powder X-ray diffraction pattern. The elemental analysis showed no solvent molecules. The results showed that the H-pair crystallized in the same crystal form (H0-form) without solvent molecules.

**Physicochemical Analyses of Three Crystal Forms (L-Form, H-Form and MA-Form)** The powder X-ray diffraction patterns of the three crystal forms (L1-form, H0-form, MA2-form) are compared in Fig. 3. The three intensive peaks of the MA2-form ($2\theta$=5.1, 18.0, 21.4°) were slightly different from those of the H0-form ($2\theta$=5.4, 17.6, 19.7°), while the diffraction pattern of the L1-form ($2\theta$=8.6, 10.8, 19.6°) was completely different from those of MA2 and H0-forms.

The DSC curves for the three crystal forms are shown in Fig. 4. The H0-form showed only one endothermic peak at 190 °C due to melting, and the L1-form had one endothermic peak at 120 °C, indicating melting. The endothermic peak of dehydration cannot be observed. The MA2-form showed a broad endothermic peak in the range of 40—100 °C due to dehydration of two water molecules as determined from TG-DTA measurements. The two endothermic peaks at 175 and 185 °C were assumed to be due to the melting of the produced dehydrate form.

**Humidity-dependent Transformation between MA2-Form and MA0-Form** The DSC curve suggests that the MA2-form was transformed to the dehydrate form by dehydration. Therefore the volatilization of the MA2-form was investigated under low humidity conditions (30% RH) at room temperature using powder X-ray diffraction and thermal analysis. Powder X-ray profiles and DSC thermograms after dehydration are summarized in Figs. 5 and 6, respectively. The characteristic diffraction peaks of the MA2-form decreased and new diffraction peaks appeared. The resulted pattern was very similar to that of the H0-form. This indicates that the dehydrate form is crystalline, which is called the MA0-form. The broad endothermic peak due to dehydration in the DSC curve disappeared. The DSC curve of the dehydrated form was different from that of the H0-form. Then the produced MA0-form was converted into the MA2-form at high relative humidity of 80% at 25 °C. The transition between the MA2-form and MA0-form was reversible. Although the H0-form had a similar X-ray pattern, it showed no transformation under high humidity.

**Crystal Structure of Dehydrated MA0-Form and Comparison with MA2-Form and H0-Form** Crystal data and the experimental details are given in Table 2. The crystal and molecular structures of the MA0-form at −50 °C are shown in Figs. 7 and 8, respectively. The two water molecules in the MA2-form crystal completely disappeared. The molecular structure was disordered because it is composed of the H-

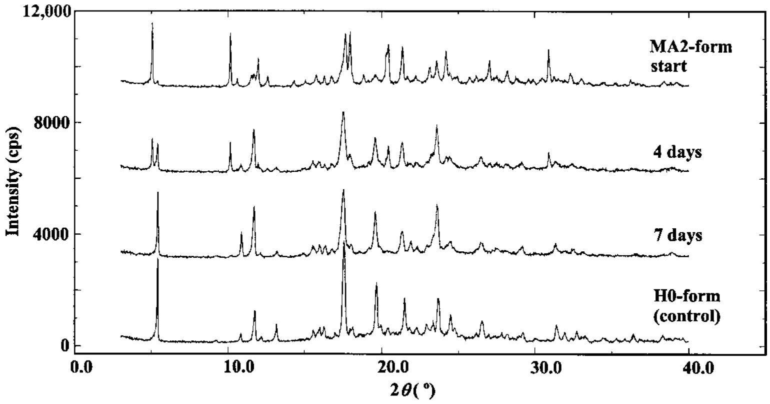

Fig. 5. Changes in the Powder X-Ray Diffraction Pattern of the MA2-Form by Storing at Low Humidity

The most characteristic peak of the MA2-form seen at 5.1° (2$\theta$) shifted at 5.4° (2$\theta$). Finally, the MA2-form was transformed into the MA0-form that has a similar diffraction pattern to the H0-form.

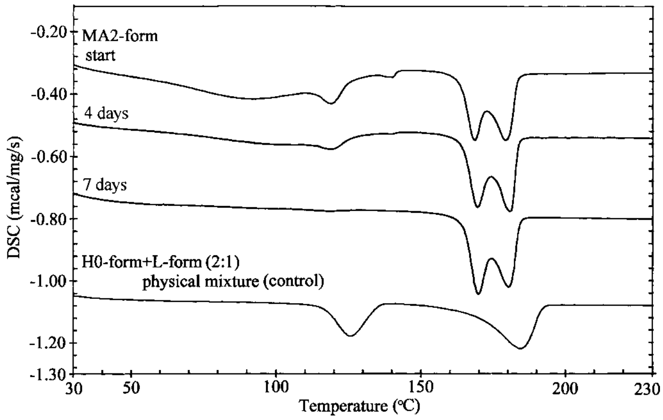

Fig. 6. Changes in the DSC Thermogram of the MA2-Form by Storing at Low Humidity

Table 2. Crystal and Experimental Data of the Three Crystal Forms

| Crystal form | MA2-form | MA0-form | H0-form |
|---|---|---|---|
| Chemical form | Dihydrate | Dehydrate | Anhydrate |
| Formula | $C_{24}H_{27}O_5NS \cdot 2H_2O$ | $C_{24}H_{27}O_5NS$ | $C_{24}H_{27}O_5NS$ |
| Formula weight | 477.56 | 441.53 | 441.53 |
| Instrument | R-AXIS RAPID | R-AXIS RAPID | R-AXIS RAPID |
| Radiation (Å) | Mo$K\alpha$, 0.71069 | Mo$K\alpha$, 0.71069 | Mo$K\alpha$, 0.71069 |
| Temperature (°C) | −50 | −50 | −50 |
| Size (mm$^3$) | 0.25×0.35×0.05 | 0.25×0.35×0.05 | 0.30×0.40×0.10 |
| Crystal form, color | Plate, colorless | Plate, opaque | Plate, colorless |
| Crystal system | Monoclinic | Monoclinic | Monoclinic |
| Space group | $P2_1$/c | $P2_1$/c | $P2_1$/c |
| Cell constant | | | |
| $a$ (Å) | 17.3380 (4) | 16.236 (1) | 16.3582 (3) |
| $b$ (Å) | 11.7667 (3) | 11.5989 (8) | 11.6077 (2) |
| $c$ (Å) | 11.5835 (3) | 11.7672 (9) | 11.5399 (2) |
| $\beta$ (°) | 94.028 (1) | 93.481 (3) | 93.873 (1) |
| $V$ (Å$^3$) | 2357.3 (1) | 2211.9 (3) | 2186.20 (7) |
| $Z$ | 4 | 4 | 4 |
| Calc. density (g/cm$^3$) | 1.346 | 1.326 | 1.341 |
| Restraints | 6 | 0 | 0 |
| No. of reflections | 5401 | 4565 | 5000 |
| No. of reflections used | 4815 | 3273 | 4492 |
| Parameters | 481 | 433 | 361 |
| $R1$ (%) | 4.9 | 6.8 | 4.1 |
| $_{w}R2$ (%) | 12.1 | 17.8 | 11.0 |
| Goodness of fit | 1.12 | 1.04 | 1.06 |
| Structure determination | SIR97 | SIR97 | SIR97 |
| Refinement program | SHELXL-97 | SHELXL-97 | SHELXL-97 |

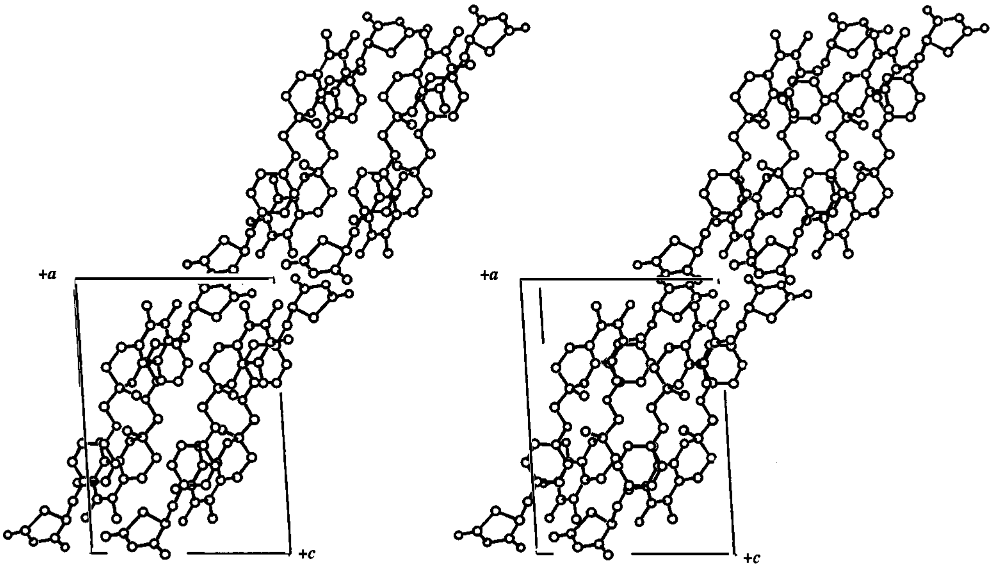

Fig. 7. Stereoview of Crystal Structure of the MA0-Form

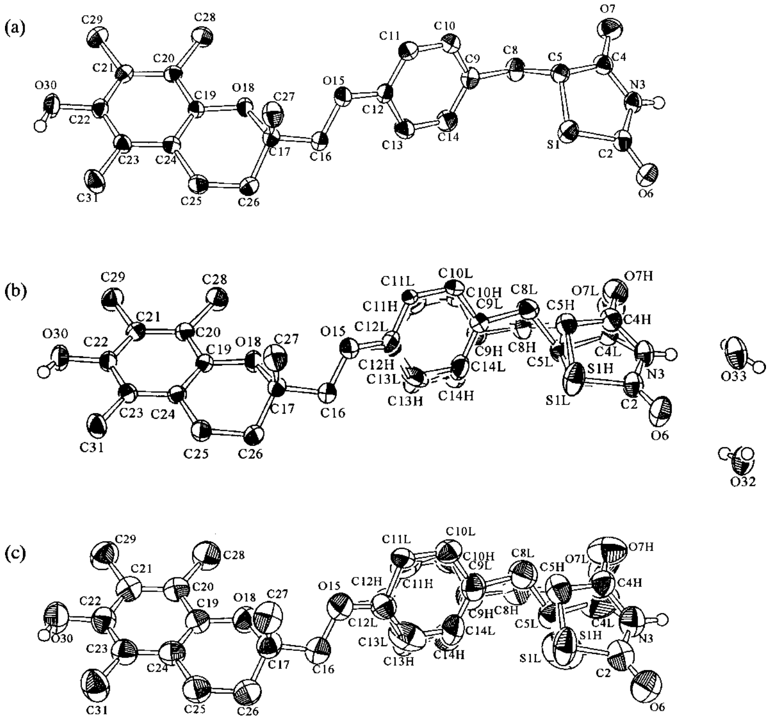

Fig. 8. Molecular Structure of Three Polymorphic Forms

(a) H0-form; (b) MA2-form; (c) MA0-form. Non-hydrogen atoms are shown as ellipsoids at 50% thermal probability level.

and L-pair.

Although the crystal structures of the MA2-form[14] and the H0-form[18] at 23.5 °C were previously reported, they were analyzed again at −50 °C, to obtain the disordered structure more precisely and compare the structures with that of the MA0-form more minutely. The crystal data and experimental detail of the MA2 and H0-forms at −50 °C are also given in Table 2. The molecular structures of the three crystal forms are shown in Fig. 8. The disordered molecular structures of MA2 and MA0-forms are composed of the H- and L-pair compounds. Based on the occupancy factors of the corresponding atoms of thiazolidine ring and benzyl group moiety, the MA0- and MA2-forms have the H- and L-pairs in the ratios of 67 : 33 and 64 : 36, respectively. However, the peripheral atoms of the disordered moieties, N3, C2, and O6, occupy nearly the same positions. This indicates that the same hydrogen bonds can be formed between the molecules for both the H- and L-pair molecules. The H-pair molecules had approximately the same conformation among the three forms.[14]

Two water molecules of the MA2-form occur between the molecules and form hydrogen bonds with both sides of the molecules. The molecules are connected as a straight chain. The molecular chains are piled up two dimensionally by the hydrogen bonds between the water molecules. The MA2-form has a hydrogen bond network, for which the distances are listed in Table 3.

When the two water molecules are removed from the MA2 crystal, the two molecules along the a axis in the MA0 crystal come into proximity and are connected with the two hydrogen bonds of N3–H3···O30 and O30–H30···O6, as shown in Fig. 9. This causes the contraction of the *a*-axis length by 1.10 Å. However, the crystal lattice is maintained in the process of dehydration and the crystal structure after

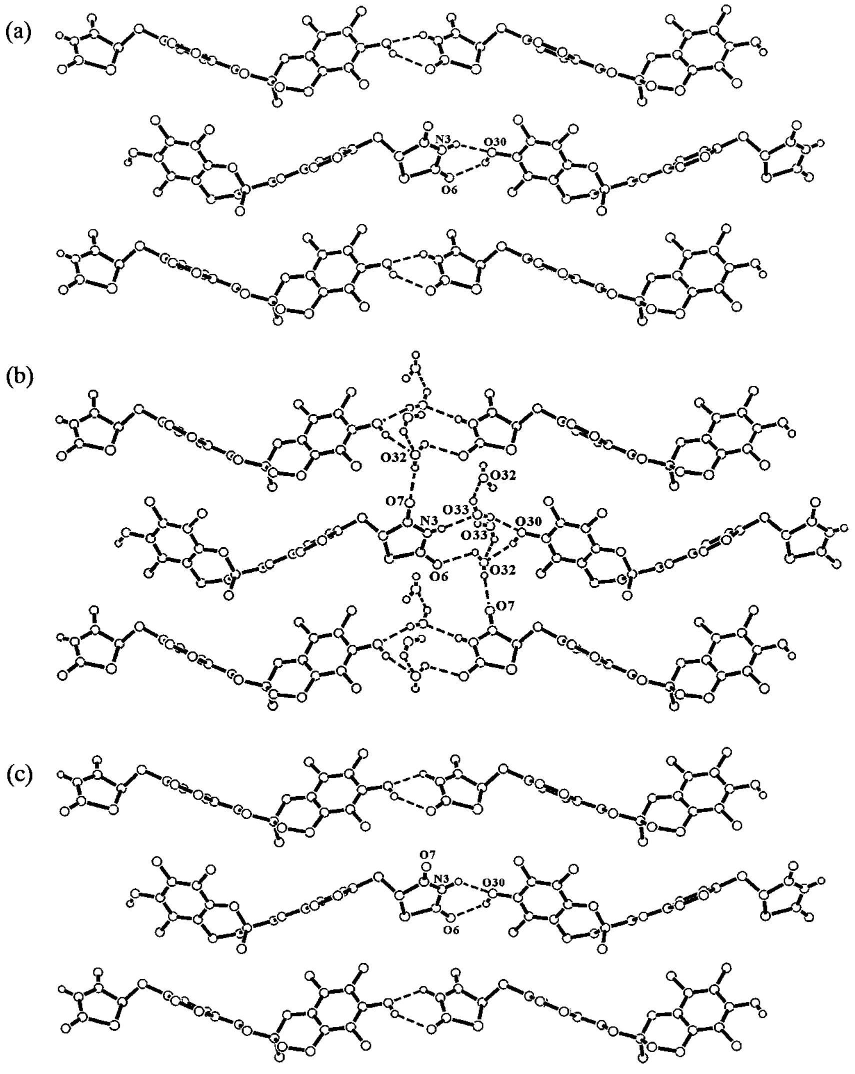

Fig. 9. Packing of Molecules in the Three Crystal Forms

(a) H0-form; (b) MA2-form; and (c) MA0-form. The MA2-form and MA0-form are disordered crystals consisting of each isomer. The minor part was omitted in Figs. 9b, c.

Table 3. Hydrogen Bonding System of the Three Crystal Forms (Å, °)

| Atom | Atom | Atom | D–H | H···A | D···A | ∠DHA | Symmetry |
|---|---|---|---|---|---|---|---|
| MA2-form | | | | | | | |
| N3 | – H3 | ··· O33 | 0.81 (2) | 2.08 (2) | 2.884 (2) | 175 (2) | +*x*, +*y*, +*z* |
| O30 | – H30 | ··· O32 | 0.84 (3) | 1.96 (3) | 2.770 (2) | 159 (2) | −1+*x*, +*y*, 1+*z* |
| O32 | – H32a | ··· O6 | 0.74 (2) | 2.43 (3) | 2.788 (2) | 111 (2) | +*x*, +*y*, −1+*z* |
| O32 | – H32b | ··· O7H | 0.75 (2) | 2.06 (2) | 2.81 (1) | 172 (3) | 2−*x*, −1/2+*y*, −1/2−*z* |
| O32 | – H32b | ··· O7L | 0.75 (2) | 2.14 (2) | 2.88 (2) | 167 (3) | 2−*x*, −1/2+*y*, −1/2−*z* |
| O33 | – H33a | ··· O30 | 0.76 (2) | 2.39 (2) | 3.117 (2) | 161 (3) | 1+*x*, +*y*, −1+*z* |
| O33 | – H33b | ··· O32 | 0.76 (2) | 2.71 (3) | 3.016 (2) | 107 (2) | 2−*x*, 1−*y*, −1−*z* |
| MA0-form | | | | | | | |
| N3 | – H3 | ··· O30 | 0.99 (4) | 2.08 (3) | 2.830 (4) | 131 (3) | 1+*x*, +*y*, 1+*z* |
| O30 | – H30 | ··· O6 | 0.80 (4) | 2.15 (4) | 2.816 (3) | 142 (4) | −1+*x*, +*y*, −1+*z* |
| H0-form | | | | | | | |
| N3 | – H3 | ··· O30 | 0.84 (2) | 2.10 (2) | 2.813 (2) | 141 (2) | 1+*x*, +*y*, 1+*z* |
| O30 | – H30 | ··· O6 | 0.80 (2) | 2.15 (2) | 2.812 (2) | 140 (2) | −1+*x*, +*y*, −1+*z* |

Table 4. Crystal and Experimental Data of the Four Crystal Forms of the L-Pair Compound

| Crystal form | L1/2-form | | | L1-form[19] |
|---|---|---|---|---|
| Chemical form | 1/2MeCN solvate | 1/2MeOH solvate | 1/2EtOH solvate | Monohydrate |
| Formula | $(C_{24}H_{27}O_5NS)_2 \cdot C_2H_3N$ | $(C_{24}H_{27}O_5NS)_2 \cdot CH_4O$ | $(C_{24}H_{27}O_5NS)_2 \cdot C_2H_6O$ | $C_{24}H_{27}O_5NS \cdot H_2O$ |
| Formula weight | 924.13 | 915.12 | 921.15 | 459.56 |
| Instrument | MAC MXC | MAC MXC | MAC MXC | Rigaku AFC7 |
| Radiation | Cu$K\alpha$ 1.57148 | Mo$K\alpha$ 0.71069 | Mo$K\alpha$ 0.71069 | Cu$K\alpha$ 1.54178 |
| Temperature (°C) | 23.5 | 23.5 | 23.5 | −105 |
| Size (mm$^3$) | 0.60×0.30×0.15 | 0.30×0.20×0.10 | 0.35×0.30×0.20 | 0.20×0.15×0.05 |
| Crystal habit, color | Prism, colorless | Prism, colorless | Prism, colorless | Plate, colorless |
| Crystal system | Triclinic | Triclinic | Triclinic | Triclinic |
| Space group | $P\bar{1}$ | $P\bar{1}$ | $P\bar{1}$ | $P\bar{1}$ |
| Cell constant | | | | |
| $a$ (Å) | 9.706 (3) | 9.70 (5) | 9.931 (9) | 9.565 (4) |
| $b$ (Å) | 14.826 (3) | 14.63 (3) | 14.645 (8) | 14.708 (3) |
| $c$ (Å) | 16.565 (2) | 16.51 (1) | 16.60 (1) | 16.511 (3) |
| $\alpha$ (°) | 97.17 (1) | 98.15 (8) | 97.06 (5) | 98.75 (2) |
| $\beta$ (°) | 87.00 (2) | 85.6 (1) | 86.72 (8) | 85.26 (2) |
| $\gamma$ (°) | 92.78 (2) | 92.0 (2) | 91.20 (6) | 92.82 (2) |
| $V$ (Å$^3$) | 2359.6 (9) | 2313 (8) | 2391 (3) | 2286 (1) |
| $Z$ | 4 | 4 | 4 | 4 |
| Calc. density (g/cm$^3$) | 1.358 | 1.313 | 1.279 | 1.335 |
| Restraints | 0 | 0 | 0 | 0 |
| No. of reflections | 7566 | 6468 | 6834 | |
| No. of reflections used | 6848 | 3305 | 4020 | 4232 |
| Parameter | 803 | 794 | 803 | |
| $R$ (%) | 5.5 | 6.0 | 6.6 | 4.3 |
| $R_w$ (%) | 5.4 | 6.3 | 6.6 | 4.2 |
| Goodness of fit | 2.10 | 1.66 | 1.91 | 1.57 |
| Structure determination | SIR92 | SIR92 | SIR92 | SIR92 |
| Refinement program | CRYSTAN 6.3.3. | CRYSTAN 6.3.3 | CRYSTAN 6.3.3 | teXsan 1.8. |

*a*) The data for the L1-form were reported in ref. 19.

dehydration was analyzed successfully. Since the MA0-form has a similar orientation in the MA2-form (Figs. 9b, c), even though the water molecules of the MA2-form are released, the resulting crystal structure of the MA0-form enables it to adopt the hydrogen bond system of the H0-form.

The MA0-form had a similar molecular structure to the H0-form (Figs. 8a, c). Since both the H- and L-pair molecules of the MA0-form can form hydrogen bonds to align the molecules in the same molecular chain as that of the MA2-form, dehydration can proceed without destroying the crystallinity, and a similar crystal structure may be produced after dehydration.

**Structural Relationship between the L1-Form and L1/2-Form** The crystal structure of the L1-form was previously reported.[19] The crystallographic data and the experimental details of the three L1/2-forms are listed in Table 4. The L1/2-form including dichloromethane was too quickly decomposed due to desolvation to obtain the intensity data. The L1/2-forms of methanol and ethanol were gradually decomposed during data collection and the number of reflections observed decreased.

Since the L1-form and the three L1/2-forms are isomorphous to each other, only the crystal structures of the L1-form and L1/2-form with acetonitrile are shown in Fig. 10. There are two L-pair troglitazone molecules in an asymmetric unit of the $P\bar{1}$ cell. There is a wide space between the molecules, which is occupied by two water molecules in the L1-form (Fig. 10a) or with one solvent molecule in the L1/2-form (Fig. 10b). Although the two water molecules in the L1-form form hydrogen bonds with the neighboring troglitazone and water molecules, they appear to occupy the void space surrounded by the troglitazone molecules. The molecular structures of the L-pair in the L1-form and L1/2-form are substantially the same as each other, but are different from that of the L-pair in the MA2 and MA0-forms. The L-pair molecule has a different conformation around the C16–C17 bond between the L-forms and the MA-forms: the torsion angles of O15–C16–C17–O18 are the *anti* conformation [L1/2-form (MeCN): 177.2 (2)°, 175.2 (2)°, L1-form: 173.4 (3)°, 177.6 (3)°)]], while the L-pair molecules in the MA0- and MA2-forms, have the *syn* conformation [torsion angles 67.8 (3)° and 67.5 (3)°)].

## Conclusions

Troglitazone has two diastereomer pairs, the H-pair and L-pair. The H-pair isomer crystallized only an anhydrate crystal, the H0-form. The L-pair diastereomer produced solvate crystals with various solvent molecules: for methanol, ethanol, acetonitrile, and dichloromethane, the L1/2-forms in which there are one solvent molecule and two troglitazone molecules in an asymmetric unit cell; and for water, the L1-form in which there are two water molecules and two troglitazone molecules. The L1-form showed only one endothermic peak in the DSC measurement due to melting of the crystal. The mixed crystal containing two diastereomer pairs, the H-pair and the L-pair, was formed from an aqueous solution as a dihydrate, the MA2-form. The crystal structure of the MA2-form was similar to that of the H0-form.

When the MA2-crystal was kept below 40% RH at room temperature, the solvent water molecules were removed from the crystal and the dehydrated crystal, the MA0-form, was produced. The MA0-form slowly converted back to the

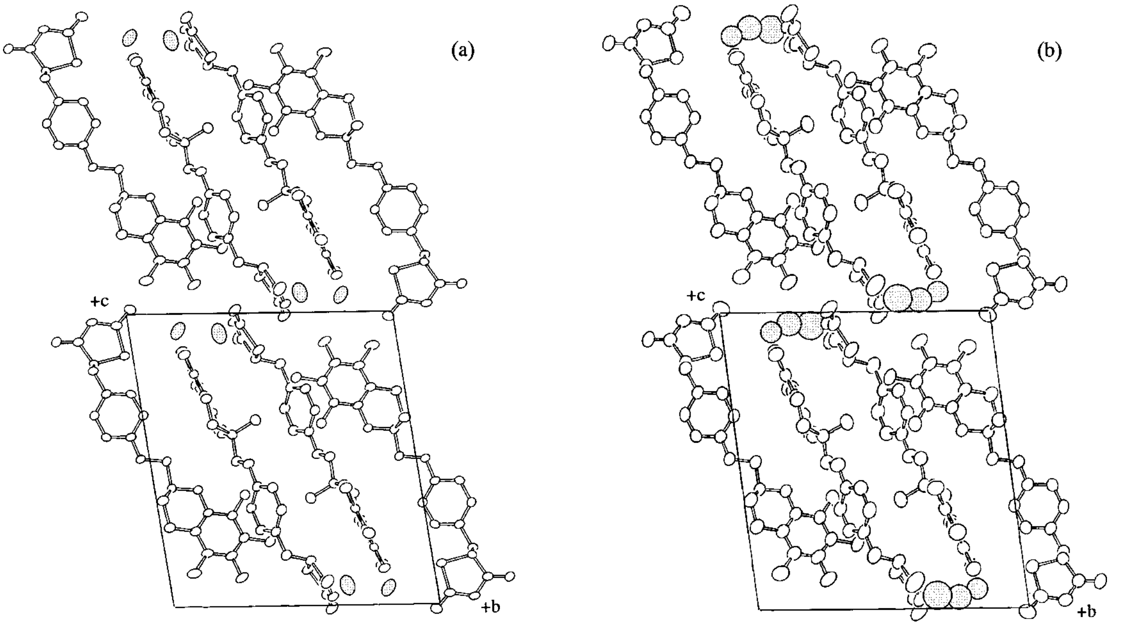

Fig. 10. Crystal Structure of the L1-Form and L1/2-Form with Acetonitrile

(a) Monohydrate; (b) acetonitrilate. Non-hydrogen atoms are shown as ellipsoids at the 50% thermal probability level. Acetonitrile molecules in the crystal packings (b) are refined with an isotropic temperature factor. The structure is projected along the *a*-axis.

MA2-form under 80% RH at room temperature. It must be emphasized that the dehydrated mixed crystal was easily converted into its dihydrate crystal and *vice versa* while retaining the single crystal form under conditions of humidity. The two solvent water molecules are inserted between troglitazone molecules and connect the molecules with hydrogen bonds to form the same molecular chain as that before hydration. The conformation of the H-pair in the mixed crystals of the MA2-form and the MA0-form was similar to that in the H0-form, whereas the conformation of the L-pair in the mixed crystals was different from those in the L1-form and the L1/2-form.

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