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Molecular Level Understanding of the Reversible Phase Transformation between Forms III and II of Dapsone

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Abstract

The reversible solid-state phase transformation between the neat forms **II** and **III** of dapsone (DDS) was studied using thermal analytical methods, variable temperature X-ray diffraction and solid-state modeling at the electronic level. The first order **III** $\leftrightarrow$ **II** phase transformation occurs at 78 ± 4 °C with a heat of transition of 2 kJ mol^{-1} and a small hysteresis. The two isosymmetric polymorphs (both $P2_12_12_1$) differ only in movement of layers of molecules and show a small variation in conformation. The combination of variable-temperature single-crystal structure determinations and pair-wise intermolecular energy calculations allowed us to unravel the single-to-single crystal transformation at a molecular level, to estimate the molecular contributions to the heat of transformation and to rationalize why the room and low temperature form **III** is the less dense polymorphic form, which is a rare phenomenon in enantiotropically related pairs of polymorphs in molecular crystals.

Keywords

dapsone; DDS; single-to-single crystal phase transformation; intermolecular energy calculations; thermal analysis; temperature-dependent X-ray diffraction

The knowledge of multiple crystalline forms is a central research topic in modern drug development and is a prerequisite for ensuring a high product quality and safety. This is because different solid forms of a chemically defined compound show distinct physical properties (e.g. solubility, density, hardness, melting point, *etc.*) and thus, the solid form can profoundly influence processing, storage stability and performance of a drug product.^{1, 2} Consequently, a lot of experimental³ and computational^{4, 5} efforts go into finding all

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Associated Content

Experimental section, crystallography (powder and single crystal), modeling of the form **II** and **III** structures. Crystallographic information files are also available from the Cambridge Crystallographic Data Centre (CCDC) upon request (<http://www.ccdc.cam.ac.uk>, CCDC deposition numbers 1566767–1566772). This information is available free of charge via the Internet at <http://pubs.acs.org>.

Author Contributions

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relevant solid forms, examining the kinetics and thermodynamic stabilities of the crystal forms, and into establishing the most important transformation pathways.

Polymorphic phase transformations of molecular crystals are heavily studied, as demonstrated by the literature. In contrast to solvent-mediated transformations,⁶ solid-solid transformations are normally associated with relatively high energy barriers due to hindrance in molecular rearrangement in the solid-state. Mechanisms for solid-solid transformations are still debated, with the classical nucleation-and-growth concept by Mnyukh being one of the proposed models. The latter implies a crystal growth by nucleation encoded in crystal defects and a subsequent molecule-by-molecule relocation at the interfaces. At the interface there is a net of microcavities that cannot accommodate additional molecules. Thus, no essential lattice distortion occurs.^{7, 8} In the case of a polymorphic pair with similar crystal structures such as D,L-norleucine^{9,10}, a displacive transition with cooperative motion¹¹ may characterize the type of the transformation reaction.

Dapsone (4,4'-diaminodiphenyl sulfone; DDS, Figure 1), synthesized for the first time in 1908,¹² is an aniline derivative and belongs to the class of synthetic sulfones. The microbial activity of the compound was recognized 80 years ago. To date, dapsone has been in use for the treatment of a diversity of diseases including leprosy, dermatitis herpetiformis, malaria and in the prophylaxis of pneumocytosis. The sulfone still is of prime importance in the treatment against mycobacterium leprae.^{13, 14} Several attempts have been undertaken to overcome its solubility limitation, e.g. inclusion compounds with β -cyclodextrine,¹⁵ nanoemulsion formulations¹⁶ or co-crystal formation^{17–19}.

Since the late 1970s, the pure drug compound has been known to exist in four anhydrous forms which are denominated with roman numerals in the order of their melting points, **I**: 179 °C, **II**: 177 °C, **III**: transforms to **II** upon heating and **IV**: ~170 °C).²¹ Form **I** was identified as the high temperature form and form **III** as the most stable polymorph of the four forms present in commercial products and enantiotropically related to form **II** and form **I**. Form **IV** is a metastable phase obtained concomitantly with form **III** upon tempering the quench cooled melt < 70 °C and exhibiting low kinetic stability.^{20, 21} Furthermore, a 0.33-hydrate^{22–24} and three solvates^{25, 26} (a hemisolvate with dichloromethane and two monosolvates with 1,4-dioxane and tetrahydrofuran) have been reported. Crystal structures of form **III**^{27–31}, the hydrate^{22–24} and the three solvates^{25, 26} have been determined.

Here, we report the results of a study of the reversible solid-state phase transformation between the forms **II** and **III**, unravelling the transformation at a molecular level by combining thermal analysis (hot-stage microscopy and differential scanning calorimetry) and temperature-dependent X-ray diffraction (powder and single crystal) with electronic structure calculations (intermolecular interactions^{32, 33} and dispersion corrected density functional calculations³⁴).

Crystallization of DDS from organic solvents with low water activity ($a_w = 0.64$) results in crystals of form **III** showing a platy morphology. Heating induces a solid-solid transformation of form **III** into form **II** at temperatures slightly above 80 °C (Figure 2a). On cooling, the back-transformation to form **III** occurs below 80 °C (Figure 2b). The highly

reversible solid-solid transformation is indicated by changes in interference colors as observable by polarized light hot-stage microscopy (Figure 2c).

The differential scanning calorimetry (DSC) curve of DDS form **III**, recorded upon heating, shows a transformation to form **II** with an onset temperature at 81.5 ± 0.2 °C and a heat of transformation of 2.06 ± 0.06 kJ mol⁻¹ (Figure 3, first curve). The melting of form **II** was recorded at 177.2 ± 0.1 °C with a heat of fusion of 21.40 ± 0.10 kJ mol⁻¹ (third curve). The reversibility of the transition **III** $\leftrightarrow$ **II** is illustrated in the DSC curves in the temperature range starting from 70 to 90 °C. The first curve shows the endothermic transition **III** to **II** on heating. In the following cooling run (second curve) the exothermic back-transformation of form **II** to **III** is observed at temperatures below 80 °C, confirming reversibility of the transition and the enantiotropic³⁵ relationship between this pair of polymorphs. The **III** $\leftrightarrow$ **II** transformations show a rather small hysteresis and exhibit sharp transition peaks indicating that the activation barrier of the reaction is low.

The thermal analytical investigations were correlated with structural changes to the **III** $\leftrightarrow$ **II** transformations using variable-temperature powder (PXRD) and single crystal X-ray diffraction experiments. In agreement with the DSC results (Figure 3), the PXRD patterns start to change at 80 °C (Figure 4a) upon heating. Though clear changes in peak positions and intensities are observed, the structural similarity between the two phases is obvious from their PXRD patterns. The variable temperature diffraction patterns were indexed using the first 20 peaks with DICVOL04 and the space group was determined based on a statistical assessment of systematic absences,³⁶ as implemented in the DASH structure solution package.³⁷ Pawley fits³⁸ were performed with Topas Academic V5.³⁹ The lattice parameters and space group of form **III** agree with its single crystal data ignoring temperature effects. Form **II** (Figure 4a,b – red diffractograms) crystallizes with the same space group symmetry as form **III**, $P2_12_12_1$, which was additionally confirmed by solving the structure from single-crystal diffraction data. A comparison of the lattice parameters, determined from the series of PXRD patterns collected in heating and cooling experiments, reveals that the *a* and *b* axis, as well as the cell volume, decrease during the **III** to **II** phase transformation discontinuously, while the *c* axis increases (Figure 4c-f). Form **II** exhibits a smaller cell volume than form **III** (at the transition point), which means that form **II** is more densely packed. This transition to a denser high temperature phase is surprising as the density rule⁴⁰ would suggest that the high temperature form in an enantiotropic system (form with the higher zero point energy) exhibits a lower density than the (at 0 K) thermodynamically stable form, which has been verified in other pairs of enantiotropically related polymorphs such as cinacalcet HCl,⁴¹ D,L-norleucine,^{9,10} or ethambutol hydrochloride.⁴²

The lattice parameters extracted from the LeBail-fits have been employed to calculate the thermal expansion tensor α_{ij} for form **III** and **II** in the infinitesimal temperature limit using the program TEV.⁴³ A thorough inspection of the evolution of the individual lattice parameters as a function of temperature revealed that all of them can be satisfactorily described in the relevant temperature intervals (30 – 80 °C for form **III** and 90 – 120 °C for form **II**) by first-order polynomials. In more detail, the following relationships have been obtained:

Form **III**: $a(T)=8.0509 + 3.6961 \cdot 10^{-4} \cdot T$, $b(T)=25.534 - 4.1659 \cdot 10^{-5} \cdot T$, $c(T)=5.7445 + 7.1208 \cdot 10^{-4} \cdot T$

Form **II**: $a(T)=7.9408 + 5.8257 \cdot 10^{-4} \cdot T$, $b(T)=25.062 + 0.0012968 \cdot T$, $c(T)=5.7871 + 8.5164 \cdot 10^{-4} \cdot T$

The abovementioned calculations resulted in the following components of the α_{ij} -tensor for the two forms for two selected temperatures⁴³:

$$\alpha_{ij}^{FormIII, 50^\circ C} = \begin{pmatrix} 4.580 & 0 & 0 \\ 0 & -0.163 & 0 \\ 0 & 0 & 12.320 \end{pmatrix} \times 10^{-5} \quad \alpha_{ij}^{FormII, 100^\circ C} = \begin{pmatrix} 7.283 & 0 & 0 \\ 0 & 5.148 & 0 \\ 0 & 0 & 14.503 \end{pmatrix} \times 10^{-5}$$

Notably, for orthorhombic symmetry the three axes of the orthogonalized reference system $\{\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3\}$ coincide with the crystallographic axes $\{a, b, c\}$. From the comparison of the numerical values it is obvious that thermal expansion in form **III** is highly anisotropic. Actually, the small negative value of α_{22} indicates a slight contraction of the structure along b upon heating. The most pronounced thermal expansion occurs parallel to c whereas α_{11} has an intermediate value. The direction of greatest expansion (α_{33}) is retained in form **II**. The values of α_{11} and α_{22} in form **II**, however, are both positive and have comparable numerical values, i.e. the degree of anisotropy is reduced. By plotting the thermal expansion coefficients as a function of all directions one obtains a convenient geometric representation of the anisotropic behavior of the tensor in form of a surface in three-dimensional space (Figure 5). The corresponding two-dimensional sections ($\mathbf{e}_1$ - $\mathbf{e}_2$, $\mathbf{e}_2$ - $\mathbf{e}_3$ and $\mathbf{e}_1$ - $\mathbf{e}_3$) are presented in Figure S1 of the Electronic Supporting Information.

To obtain a molecular level insight into the **III** to **II** phase transformation we performed variable temperature single-crystal X-ray diffraction experiments. The form **III** structure was redetermined at room temperature (31 °C) prior to heating the single crystal in 10 °C steps from 60 to 100 °C. In agreement with the PXRD results form **III** was present up to 80 °C and form **II** starting from 90 °C (Table S1 of the Electronic Supporting Information). DDS form **III** crystallizes in the orthorhombic space group $P2_12_12_1$ with $Z' = 1$, which is in agreement with the previous structure determinations.^{27–31} The dapsone molecule in form **III** adopts a conformation which is related to the gas phase minimum of the compound, with dihedral ϕ_4 (Figure 1 and Table S4) showing the biggest deviation from the global conformational energy minimum. Albeit selected dihedral angles differ by up to 13.5 °, the intermolecular energy difference (E_{intra}) with respect to the gas phase minimum is less than 2 kJ mol⁻¹, calculated at the B3LYP/6-31G(d,p) level of theory (section 7 of the Electronic Supporting Information).

DDS features H-bonding donor (two amino groups) and H-bonding acceptor groups (amino and sulfone groups). Each of the amino group forms one N-H $\cdots$ O interaction to a sulfone oxygen atom, leading to two C(8) chains⁴⁴, mediated by translation along a or 2_1 symmetry, respectively (Figure S1). The two N-H $\cdots$ O interactions differ significantly in lengths (N $\cdots$ O distance: 2.954(4) Å and 3.315(5) Å at 31 °C). Thus, the second may not qualify as a hydrogen bond. A third, weaker H-bonded chain, C(2), involves one of the two amino

groups and is mediated by 2_1 symmetry. To rationalize the contributions of the dapsone interactions/close contacts to its lattice energy we calculated the intermolecular energies and graphically represent their ‘energy frameworks’^{45,46} (Figure 6a,b). Interestingly, the strongest intermolecular interaction energies between pairs of dapsone molecules do not involve the strong N–H $\cdots$ O hydrogen bond (contact 3 in Figure 6a). The strongest pair wise interaction (ca. 40 kJ mol⁻¹, denoted interaction 1, Table 1 and Table S6) has the longer N–H $\cdots$ O contact. A subdivision of the energetic contributions into classical electrostatic (E_E), polarization (E_P), dispersion (E_D) and exchange-repulsion energy (E_R) reveals that dispersion forces are the major contributor to the strength of intermolecular interactions 1, 2, 4 and 6 and electrostatics to interactions 3 and 5 (both show H-bonding).

Based on the energy framework representations given in Figure 6a,b DDS form **III** can be described as a layer structure, with layers (A, B) being composed of strongly interacting dapsone molecules (interactions 1-4, Table 1). Adjacent layers interact through the N–H $\cdots$ N close contacts (interaction 5) and interaction 6, which exhibits N–H $\cdots\pi$ close contacts.

Similar to form **III**, DDS form **II** crystallizes in the same orthorhombic space group $P2_12_12_1$ with $Z' = 1$. The two polymorphs differ slightly in the conformation of the dapsone molecules (Table S5, Figure 6e), which corresponds to less than 1.5 kJ mol⁻¹ in intramolecular energy (E_{intra}). A structure comparison of forms **III** (80 °C) and **II** (90 °C) reveals a high degree of structural similarity, with a rmsd₃₀ value⁴⁷ of only 0.445 Å (Figure 7). Furthermore, the lattice parameters of the two structures were determined to differ by less than 1.5% in lengths.

Nevertheless, the phase transformation, as unambiguously indicated with thermal analytical methods, can also be followed in the diffraction experiments. The phase transformation may be simply described by a slight change in conformation (Figure 6e) and a slight shift of every alternate layer (Figure 6c), resulting in a more densely packed form **II** structure. This mechanism, involving hardly any structural disruption, is in agreement with the fast transition kinetics and a transformation energy of 2 kJ mol⁻¹, as seen in the DSC experiments. Figure 8 graphically illustrates the course of the energy for each of the six key pair-wise molecular interactions in forms **III** and **II** in the temperature range starting from 60 °C to 100 °C. Biggest relative changes in energy contributions seen between the two polymorphs involve interactions 3, 5 and 6. Overall, the classical electrostatic contributions to the lattice energy decrease in form **II** relative to form **III**, whereas the contributions arising from dispersion forces increase and compensate the loss of the short form **III** N–H $\cdots$ O (interaction 3) and N–H $\cdots$ N (5) interactions (Figure 6a-d) in form **II**. Thus, the energy change seen for interaction 3 arises from the fact that the short form **III** N–H $\cdots$ O interaction is not formed any longer in **II**. Changes observed for interactions 5 and 6 can be related to the shift of the dapsone layers with respect to each other, with the form **III** and **II** combinations of interactions 5 and 6 being almost isoenergetic.

A comparison of cluster energies of the forms **II** and **III**, which roughly correspond to the lattice energies (Figure 8, intermolecular energy contributions of a central dapsone molecule and its 12 nearest neighbors – first coordination sphere), clearly indicates the change in

stability order from **III** to **II** upon heating, in agreement with the experimental phase transformation.

Despite the structural, conformational and packing similarities (Figure 6 and Figure S2) of the two forms, the polymorphic pair **II/III** represents (another) exception to the density rule.⁴⁸ It should be emphasized that cases of enantiotropically related forms, where the highly reversible transition to the high temperature structure is associated with an increase in density are particularly rare. However, a related behavior was observed for acetazolamide (AAA) forms **I** and **II**.⁴⁹ In contrast to DDS the structures of AAA are dominated by a strong hydrogen bond network, which strongly affects the kinetics (activation energy) of the solid-solid transition. Therefore, the transition of the high temperature form to the low temperature form is not observable on cooling. A structural difference between the two forms of DDS involves the loss of the strong N–H···O hydrogen bond seen in **III**, allowing for a denser packing in **II**, with dispersion forces compensating the loss of electrostatic contributions. The fact that no strong H-bonding is observed in form **II** may also explain the bigger cell volume expansion observed for form **II** upon heating in contrast to form **III** (Figure 4f).

The reversible solid-state transformation between DDS forms **II** and **III** was studied using thermal analytical methods and X-ray diffraction studies and was complemented with calculating the intermolecular energy contributions of pair-wise dapsone interactions at different temperatures. The results obtained from the combination of experimental and computational techniques lead to the conclusion that during the **III** ↔ **II** transformation a small shift of dapsone molecule layers occurs concomitantly with minor conformational changes, rationalizing the fast and highly reversible first-order solid-state transformation. The fact that the high temperature form is denser than the low temperature phase is an exceptional phenomenon in molecular crystals but can be explained and understood by analyzing the complex interplay of intermolecular energy contributions.

Supplementary Material

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Synopsis

The highly reversible **III** $\leftrightarrow$ **II** first-order solid-solid transformation, including the second structure of neat dapsone, are reported. The transformations proceed at ~ 80 °C and have been characterized by thermal analysis and X-ray diffraction. Together with intermolecular interaction energy calculations we unravel the minor but relevant relative movement of layers of molecules and minor torsional changes observed during the transformation.

Figure 1.
Molecular diagram of 4,4'-diaminodiphenyl sulfone (DDS, dapsone).

(a) heating

(b) cooling

(c) heating and cooling (single crystal)

Figure 2.

Polarized light hot-stage microscopy images of DDS. (a,b) Melt-film preparation showing (a) the **III** $\rightarrow$ **II** and (b) the reversible **II** $\rightarrow$ **III** transformations. (c) Dapsone **III** $\leftrightarrow$ **II** single-to-single crystal transformations.

Figure 3.

Differential scanning calorimetry curves showing the reversible solid-solid transformation of the DDS form **III** to form **II** (heating) and *vice versa* (cooling) recorded at a heating rate of 10 °C min⁻¹. $\text{trs}H$ – heat of transformation; $\text{fus}H$ – heat of fusion.

Figure 4.

(a,b) Temperature-dependent PXRD measurements showing the **III** (blue) $\leftrightarrow$ **II** (red) phase transformations. Arrows indicate the course of the heating/cooling experiments. (c-f) Temperature-dependent changes of the lattice parameters and cell volume of DDS forms **III** and **II** on heating and cooling.

Figure 5.

(a,b) Representation surface of the thermal expansion tensor for (a) form **III** (50 °C) and (b) form **II** (100 °C) of DDS. The crystallographic system $\{a, b, c\}$ coincides with the orthonormal system $\{e_1, e_2, e_3\}$.

Figure 6. (a-d) Energy frameworks for the crystal structures of (a,b) DDS form **III** (80 °C) and (c,d) form **II** (90 °C), viewed along the crystallographic *c* axis in (a,b) and the *a* axis in (c,d). The energy scale factor is 80, and interaction energies with magnitudes smaller than 10 kJ mol⁻¹ have been omitted. Red arrows in (c) indicate the shift of B layers with respect to (a). (e) Overlay of the dapsone molecules observed in forms **II** (red) and **III** (blue). Energy values given correspond to the intramolecular energy difference (E_{intra}) with respect to the global dapsone conformational energy minimum, calculated at the B3LYP/6-31G(d,p) level of theory.

Figure 7.

Overlay of DDS form **III** (80 °C, blue) and form **II** (90 °C, red), showing the structural similarity between the two polymorphs. $\text{Rmsd}_{30} = 0.445 \text{ \AA}$.

Figure 8.

Pair-wise intermolecular energy contributions for interactions 1-6 (Table S6 and Figure 6a-d). The intermolecular energy (E_{cluster}) for the cluster was calculated as the sum of the 12 strongest pair-wise intermolecular interactions (each of the six interactions is present twice in the crystal).

Table 1Pair-wise intermolecular interaction energies^a of DDS form **III** (31 °C).

Interaction ^b	Symmetry operation	Distance (Å)	E_E (kJ mol ⁻¹)	E_P (kJ mol ⁻¹)	E_D (kJ mol ⁻¹)	E_R (kJ mol ⁻¹)	E_{tot} ^c (kJ mol ⁻¹)
Form III, 31 °C; $E_{inter}(\text{cluster})^d = -146.6$ kJ mol⁻¹							
1 (2x)	x+1/2, -y+1/2, -z	7.02	-21.9	-5.4	-31.8	23.7	-40.3
2 (2x)	x+1/2, -y+1/2, -z	7.15	-10.9	-5.1	-31.1	17.5	-31.6
3 (2x)	x+1, y, z	8.06	-26.9	-8.3	-11.2	26.5	-28.0
4 (2x)	x, y, z+1	5.76	3.0	-5.4	-27.5	15.0	-15.5
5 (2x)	-x+1/2, -y, z+1/2	11.65	-12.8	-3.4	-12.0	16.0	-16.5
6 (2x)	-x+1/2, -y, z+1/2	8.23	-3.0	-2.6	-13.7	3.9	-14.7

^aElectrostatic (E_E), polarization (E_P), dispersion (E_D) and exchange-repulsion energy (E_R) contributions.^bEach of the listed interaction is present twice in the crystal.^c $E_{tot} = E_E + E_P + E_D + E_R$.^d $E_{inter}(\text{cluster})$ = sum of interactions 1-6.