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Polymorphism and solvation of indomethacin

Characterization of an indomethacin–tetrahydrofuran solvate leading to phase I

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Abstract Indomethacin crystallizes from solutions in tetrahydrofuran as a solvate exhibiting the mole ratio 1 indomethacin:2 tetrahydrofuran. Upon heating, desolvation into indomethacin phase I occurs through partial amorphization and transitory formation of a phase, which is different from the crystallographically known polymorphs. The X-ray powder diffraction pattern of the solvate was tentatively indexed on a triclinic lattice ($a = 31.454(5)$ Å, $b = 17.883(3)$ Å, $c = 10.551(2)$ Å, $\alpha = 70.55(2)°$, $\beta = 105.31(2)°$, $\gamma = 136.70(1)°$). Assuming $Z = 6$ (1 indomethacin + 2 tetrahydrofuran) formula units per unit cell, the solvate's specific volume is similar to the value calculated using additivity.

Keywords Indomethacin · Polymorphism · Solvation · Indomethacin–tetrahydrofuran solvate

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Introduction

Indomethacin (IMC), $C_{19}H_{16}ClNO_4$ ($M = 357.8$ g mol^{-1}), a non-steroidal indole-based derivative used in anti-inflammatory chemotherapy, is known to exhibit complex polymorphism and solvation, far from being fully characterized. Yamamoto [1] used Greek letters to indicate the polymorphs, whereas Borka [2] used Roman numerals; the latter will be used in this paper. The calorimetric data from literature have been compiled in Table 1. It can be seen that four IMC polymorphs with different melting points have been evidenced. The β-phase of Yamamoto [1] was later found to be a benzene solvate [2, 3]. Moreover, an IMC phase melting at 430.6–432 K with virtually the same melting point as Yamamoto's β-phase (431.2–433.6 K) was also called β-phase by Spychala et al. [4].

Available crystallographic data from literature are compiled in Table 2; only the crystal structures of phases I and II have been solved.

IMC solvation with various solvents has been reported: methanol [3], *tert*-butanol [3, 8, 14], acetone [8], benzene [5, 8, 15], dichloromethane [8, 15], tetrahydrofuran [8, 15], propanol [8, 15], propan-1-ol and propan-2-ol [8, 15], chloroform [8, 15], diethyloxide [8, 15], carbon tetrachloride [8, 15], cyclohexanone [15], ethanol [15], isoamyl alcohol [15], octan-2-ol [15], and cyclohexanol [15]. Nevertheless, only some IMC:solvent molar ratios have been determined; ratio 1:1 was found with methanol [3] and *tert*-butanol [3, 8, 14], while ratios 4:1 (acetone, benzene), 2:1 (tetrahydrofuran), 3:1 (propanol) and 6.66:1 (chloroform) were reported by Hamdi et al. [8].

The indomethacin–*tert*-butanol 1:1 solvate is the single solvate whose crystal structure has been solved [14]. It crystallizes in the monoclinic system, space group $P2_1/n$, and the lattice parameters at 120 K were found to be $a = 11{,}9806$ Å, $b = 12{,}2749$ Å, $c = 14{,}7679$ Å, $\beta = 91{,}561°$. The unit cell volume is $V = 2170{,}97$ Å^3 with $Z = 4$ formula units per unit cell. The indomethacin–tetrahydrofuran solvate (2 IMC:1 THF) was characterized by means of differential scanning calorimetry (DSC), and thermogravimetry (TG) coupled to IR spectrometric analysis of the emitted gases [8]. It was found that this solvate exhibits an IMC/THF molar ratio of 2:1 and leads to monoclinic IMC (phase II) through desolvation [8].

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Table 1 Calorimetric data from literature of indomethacin polymorphs: melting temperatures (T_{fus}) and heats of fusion ($\Delta_{fus}H$)

Phase	T_{fus}	$\Delta_{fus}H$	Reference
I (or γ)	433–434 K	–	[1]
	433 K	–	[2]
	431.0 K	109.5 J g^{-1}	[3]
	432–434 K	–	[4]
	427 K	8.64 kcal mol^{-1}(101 J g^{-1})	[5]
	434 K	110 J g^{-1}	[6]
	433–434 K	103 J g^{-1}	[7]
	432.2 K	103.0 J g^{-1}	[8]
	–	105.6 J g^{-1}	[9]
II (or α)	427.6–428.6 K	–	[1]
	427 K	–	[2]
	424 K	103.5 J g^{-1}	[3]
	426–427 K	–	[4]
	421 K	7.49 kcal mol^{-1} (87.6 J g^{-1})	[5]
	428 K	91 J g^{-1}	[6]
	426 K	92 J g^{-1}	[7]
	426 K	92.05 J g^{-1}	[8]
β	431–433.6 K	–	[1]
	430.6–432 K	–	[4]
III	421–422 K	–	[2]
IV (or δ)	406–407 K	–	[2]
	403.7 K	–	[3]

Data and phase assignments follow the cited references; however (i) melting temperatures assigned to phase β by Yamamoto [1] and Spychala [4] may belong to phase I, forming through desolvation of a benzene solvate that was mistaken for the β-phase [2, 3], and (ii) melting temperatures assigned by Kaneniwa et al. [5] to phases γ and α deviate from those assigned by others

The present paper is a result of a more general study into the pressure–temperature phase behaviour and polymorphism of indomethacin, which is an interesting case due to its many polymorphs. Moreover, not all polymorphs have been fully characterized, as mentioned above. In an attempt to prepare phase II, IMC was dissolved in THF and a crystalline solid, consisting of thin needles, was obtained. To verify whether this solid was solvate 2(IMC):1(THF) and the phase obtained after desolvatation was phase II, TG analysis and X-ray powder diffraction were performed. The results were not in accordance with reference [8], as described below.

Materials and methods

Indomethacin, $C_{19}H_{16}ClNO_4$ ($M = 357.8$ g mol^{-1}), of medicinal grade was obtained from Avocado, Research Chemicals Ltd, and used as received. Water free tetrahydrofuran, C_4H_8O ($M = 72.11$ g mol^{-1}), purchased from Prolabo (France), was distilled before use.

Differential scanning calorimetry experiments were performed using a Mettler-Toledo (Switzerland) 822e thermal analyzer equipped with a Huber (Germany) TC100 cooling device. Indium ($T_{fus} = 156.60$ °C, $\Delta_{fus}H = 3267$ J mol^{-1}) and zinc ($T_{fus} = 419.53$ °C, $\Delta_{fus}H = 7320$ J mol^{-1}) were used for calibration of temperature and enthalpy. Specimens were weighed with a microbalance sensitive to 0.01 mg and sealed in aluminium pans. DSC runs were performed at various heating rates.

Thermogravimetric experiments were performed with a Mettler-Toledo TGA/DSC1 SF/177 containing a SF SDTA FRS2 heat sensor and a MX 1 microbalance with a sensitivity of 0.001 mg. The TG was equipped with a Huber Ministat CC1. Except for some preliminary measurements at 10 and 5 K min^{-1}, the heating rate for TG measurements was 0.2 K min^{-1}.

High-resolution X-ray powder diffraction patterns were collected at $T = 301$ K using a CPS120 X-ray powder diffractometer from INEL (France) in transmission mode with the Debye-Scherrer geometry. The monochromatic wavelength of the incident beam was $\lambda_{CoK\alpha1} = 1.7889$ Å. Specimens were introduced in Lindemann glass capillaries (0.5 mm diameter). During data acquisition, the capillary was rotated to minimize preferred orientation of the crystallites.

Results

The indomethacin phase I diffraction pattern (see also Fig. 2) was analyzed with FullProf [16, 17], which yielded refined lattice parameters: $a = 9.3102$ (2) Å, $b = 10.9989$

Table 2 Measurement temperature and lattice constants of indomethacin polymorphs

Phase	T/K	S.G.	a/Å	b/Å	c/Å	α/°	β/°	γ/°	Z	V/Z/Å^3	Reference
I (or γ)	R.T.	P-1	9.295	10.969	9.742	69.38	110.79	92.78	2	432.9	[10]
I (or γ)	R.T.	P-1	9.31	10.81	11.00	105.77	93.00	122.48	2	436	[11]
I (or γ)	120	P-1	9.236	9.620	10.887	69.897	87.328	69.501	2	423.95	[12]
II (or α)	203	$P2_1$	5.462	25.310	18.152	90	94.38	90	6	417.01	[13]

R.T. room temperature, *S.G.* space group, *Z* molecules per unit cell, *V/Z* volume taken up in the crystal by one IMC molecule

(3) Å, $c = 9.7730(2)$ Å, $\alpha = 69.249\ (2)°$, $\beta = 110.894(2)°$, $\gamma = 92.831(3)°$, and a unit cell volume $V = 870.93(4)$ Å^3 (301 K). With the assumption that $Z = 2$ formula units in the unit cell, V/Z is 435.46 Å^3.

DSC experiments lead to a melting point of 432.6 ± 0.1 K (onset) and an enthalpy of fusion of 111 ± 2 J g^{-1} for IMC phase I. The present melting point corresponds to the values found in literature (Table 1), giving rise to a literature average melting point of 432 ± 2 K. There appear to be two distinct values for the enthalpy of fusion in literature; one around 103 J g^{-1} and one around 110 J g^{-1}. The present value corresponds to the higher estimate, suggesting that the enthalpy of fusion should be around 110 ± 2 J g^{-1}. Sublimation of IMC phase I remains negligible up to about 400 K, after which it starts to increase slowly as observed in TG measurements (see also Fig. 5). Neither in the diffraction pattern nor in the DSC curves, traces of other phases where observed in pure IMC of phase I.

A solution of IMC Phase I in THF was slowly evaporated at room temperature until a pale yellow opaque powder was obtained. Optical microscopy showed that the powder consisted of very thin needles (Fig. 1).

The X-ray diffraction pattern of gently crushed crystals is shown in Fig. 2. It was found to be different from the pattern of either phase I or phase II. The same pattern was obtained for crushed crystals in their mother liquor. The pattern in Fig. 2 was thus ascribed to an indomethacin–tetrahydrofuran solvate, whose stoichiometry was determined through TG.

Preliminary TG experiments (Fig. 3) showed that mass loss occurred soon after heating started. There were at least two distinct stages of evaporation and it continued above the melting temperature of IMC Phase I (≈433 K). This was due to heating too fast with respect to the low evaporation rate of THF.

Photographs of a solvate specimen between two glass slides (Fig. 4) were taken with an optical microscope coupled to a Mettler FP81 hot stage heated at 10 K min^{-1}. No visible change in the solvate was detected up to about

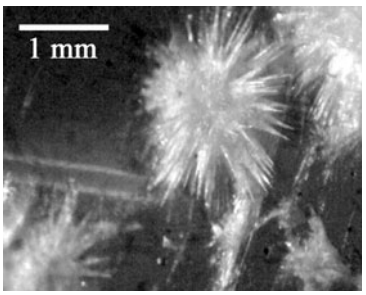

Fig. 1 Needle-shaped crystals of the indomethacin–tetrahydrofuran 1(IMC):2(THF) solvate

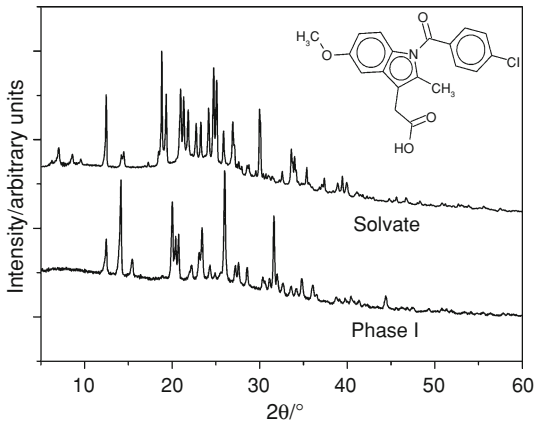

Fig. 2 High resolution X-ray diffraction pattern of the obtained indomethacin–tetrahydrofuran solvate in mother liquor (wavelength of the incident beam: $\lambda_{CoK\alpha1} = 1.7889$ Å) and for comparison the pattern of the commercial form I of indomethacin used in this study. The structure of indomethacin can be found above the two patterns

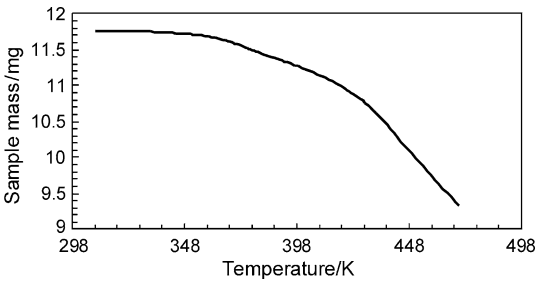

Fig. 3 Mass loss recorded on heating of the indomethacin–tetrahydrofuran solvate at a rate of 10 K min^{-1}

376 K, the temperature at which progressive melting—resembling peritectic melting—was accompanied with slow evaporation as indicated by the bubbles appearing from about 383 K.

TG experiments were conducted at 0.2 K min^{-1} with initial masses of about 1 mg with the purpose to obtain solid THF-free IMC below the phase-I melting point; the TG curves can be found in Fig. 5.

The TG curves in Fig. 5 demonstrate three distinct mass loss phenomena. The first (o–a) occurs from room temperature up to about $323 < T < 333$ K. Its presence was found to depend on the age of the solvate; for an older solvate, it was less pronounced. The second (a–b) ends at about $373 < T < 383$ K. The third mass loss (from b to c) is the slowest and must be due to either sublimation of indomethacin, or desorption of residual THF, or both. Desorption is a process, where THF has left the crystal structure of the solvate, but still remains adsorbed to the surface of indomethacin. Since the adsorption may occur inside cavities, it can be difficult for THF to leave, which leads to the tail in mass loss with a different kinetic profile than during the desolvation process.

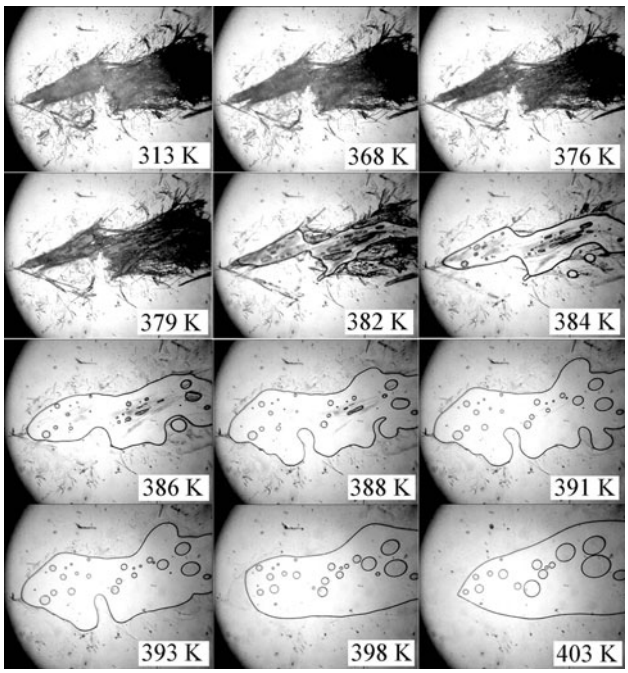

Fig. 4 Optical microscopy photographs (G ×140) taken while heating the indomethacin–tetrahydrofuran solvate at 10 K min^{-1}

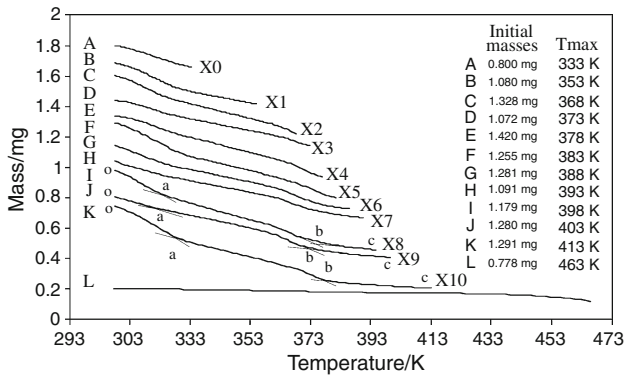

Fig. 5 TG curves recorded on heating the indomethacin–tetrahydrofuran solvate at 0.2 K min^{-1}. Curves have been shifted for clarity; the initial mass is given on the *right*. The final temperature (T_{max}) was gradually increased (curves A–K). Symbols X*i* (i = 0–10) refer to X-ray diffraction patterns obtained after the TG runs (see Fig. 6). Curve L: TG-curve recorded upon heating IMC phase I at 0.2 K min^{-1}. The specimens were weighed in with the TG microbalance, sensitive to 0.001 mg

The whole experimental mass loss between points o and c (curve K) was found to be 41.7% of the initial mass, i.e. near the value (37.68%) for a solvent-rich solvate with the 1(IMC):3(THF) mole ratio. The second mass loss (between points a and b) was found to be 24.5% of the mass at point a, i.e. close to the ideal value (28.73%) for a 1(IMC):2(THF) solvate. It is worth noting that a similar value is obtained when taking the final mass at point c instead of point b (29.2%). Similar results are obtained for the specimen heated

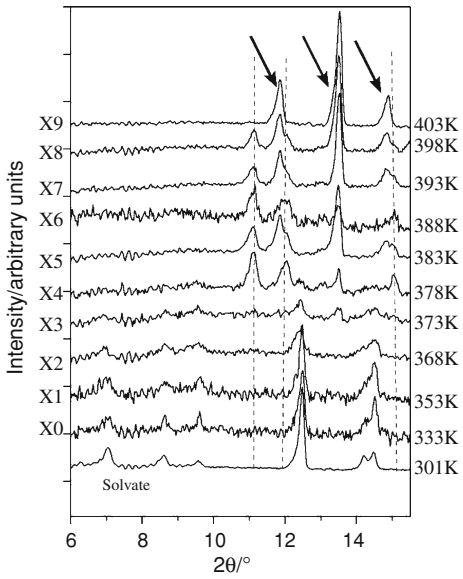

Fig. 6 Room-temperature X-ray diffraction patterns of the residue of IMC–THF solvate recovered after TG runs with increasing temperatures; 333 K (X0)–403 K (X9). The room-temperature pattern of the solvate is shown for comparison. The three *dashed lines* indicate the positions of new peaks ascribed to a transitory phase that appears from about 378 to 398 K. *Arrows* indicate which peaks are characteristic for IMC phase I

up to 403 K (curve J), which was measured a few days later. The first mass loss (o–a) can hardly be separated from the second (a–b) and together (o–b) they constitute a mass loss of 24.6%. The total mass loss of the curve accounts for 30.9%.

To investigate whether indomethacin formed different THF solvates depending on the temperature, X-ray analysis was performed on specimens subjected to TG-runs recovered at increasing maximum temperatures (Fig. 6). High-resolution X-ray powder diffraction patterns unambiguously demonstrated that the specimens recovered after heating up to 353 K are equivalent to the solvate obtained from THF at room temperature. Taking into account that the first mass loss (o–a in Fig. 5) diminishes with aging, it can be concluded that the material freshly obtained from IMC in THF solutions evaporated at room temperature is a mixture of the 1(IMC):2(THF) solvate and adsorbed THF.

X-ray powder diffraction patterns of specimens recovered from 403 K and higher temperatures were found to be those of IMC phase I. If one only considers the initial and the final state, it might be inferred that desolvation of the 1(IMC):2(THF) solvate leads to the formation of phase I. However, X-ray diffraction patterns of the intermediate steps of the process indicate that desolvation first causes amorphization superimposed on the formation of a transitory phase.

Amorphization was evidenced by a decrease of the signal over noise ratio and formation of a transitory phase

was evidenced from about 378 to 398 K by new Bragg peaks (see Fig. 6) that belong neither to the initial solvate nor to any of the known crystal structures of IMC.

Discussion and conclusions

To compare the X-ray pattern of the 1(IMC):2(THF) solvate with the pattern of the 2(IMC):1(THF) solvate reported by Hamdi et al. [8], the latter pattern was digitalized. In first instance, the two patterns did not coincide. However, after doubling the 2θ values given in Ref. [8], the patterns resembled each other closely, disregarding small differences likely due to preferred orientations and differences in data collection techniques (Fig. 7).

Single crystal structure determination of the 1(IMC):2(THF) solvate failed because of the very small size and needled shape of the crystals obtained. Unit-cell measures were obtained with program DICVOL [18] from the powder diffraction pattern recorded at 301 K. A solution was found with a triclinic lattice, which indexes all Bragg peaks in the 2θ range from 3 to 80° (see Fig. 8). Cell parameter refinement led to the following values $a = 31.454(5)$ Å, $b = 17.883(3)$ Å, $c = 10.551(2)$ Å, $\alpha = 70.55(2)°$, $\beta = 105.31(2)°$, $\gamma = 136.70(1)°$ (R-Factors: 1.19 and 1.85, χ^2: 15.7). This results in a unit-cell volume of $V = 3836.3(1)$ Å^3, in which Z, the number of formula units (1 IMC + 2 THF), is most likely an integer. V/Z is thus the volume taken up in the crystal by a single formula unit.

An estimate of V/Z for a single IMC molecule follows from the crystal structures of its polymorphs and ranges from 417 to 436 Å^3 (see Table 2). The estimate of V/Z for a single tetrahydrofuran molecule is in the order of 101 Å^3 (at 103 K) to 104 Å^3 (at 148 K) as determined by single crystal X-ray diffraction [19]. Consequently, V/Z for one

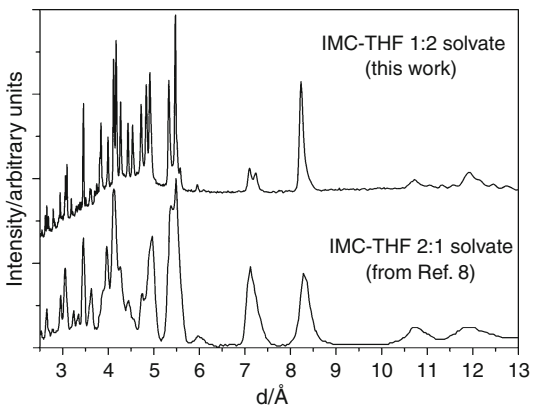

Fig. 7 Comparison of the X-ray diffraction patterns of the 1(IMC):2(THF) solvate and the 2(IMC):1(THF) solvate [8]. The 2θ values given in Ref. [8] have been doubled, and the two patterns have been drawn as a function of d(Å) values, independent of wavelength

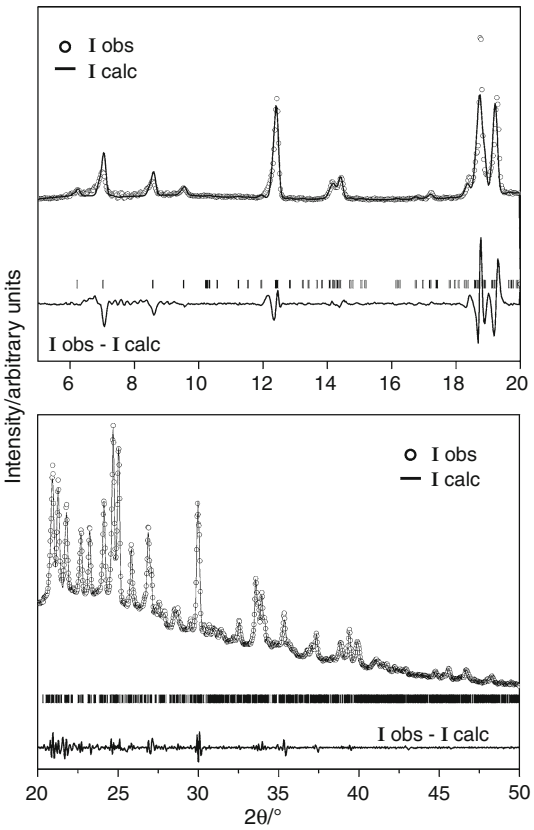

Fig. 8 Comparison between experimental and calculated patterns for the 1(IMC):2(THF) solvate. I_{obs} = observed intensity, I_{calc} = calculated intensity. The discrepancies originate from detector-related oscillations in the <10° 2θ range, that made it difficult to fit the baseline, and to some dysfunction of the detector cells in the 18.5–19.5° 2θ range

(1 IMC + 2 THF) formula unit should be about 617 to 644 Å^3 with the assumption of additivity. This leads to $Z = 6.22$ or 5.96, i.e. a value close to 6.

To verify the additivity assumption, a similar calculation was performed for the indomethacin:*tert*-butanol 1:1 solvate, whose unit-cell volume is 2170.97 Å^3 with $Z = 4$ formula units [14]. *tert*-Butanol phase IV at 295 K is triclinic [20], with a unit cell volume of 874 Å^3 and $Z = 6$, leading to $V/Z = 145.72$ Å^3. The unit-cell of the *tert*-butanol trigonal phase II has $V = 2383$ Å^3 at 220 K with $Z = 18$ [21], leading to $V/Z = 132.4$ Å^3. Thus, for solvate 1(IMC):1(*tert*-butanol), V/Z values ranging from 549 to 568 Å^3 are found, only slightly larger than the experimental value of 543 Å^3.

To conclude, an indomethacin–tetrahydrofuran solvate has been characterized and its stoichiometry has been found to be 1 indomethacin per 2 tetrahydrofuran molecules, different from the previously reported mole ratio 2:1 for an indomethacin–tetrahydrofuran solvate, which exhibits virtually the same X-ray diffraction pattern. In addition, the solvate does not lead to phase II as reported in Ref. [8] but to

phase I. Lastly, the desolvation process is accompanied with the transitory formation of a new phase, which remains to be characterized.

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