Polymorphism and versatile solvate formation of thiophanate-methyl

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The polymorphism of a fungicide, thiophanate-methyl (TM), was investigated with conventional solvent screening methods. Two polymorphs, the thermodynamically most stable form I and the less stable form II, were found. TM was also found to crystallize as plethora of different solvates which produced mostly form II upon desolvation. The structures of form I and form II and the fourteen discovered solvates were solved by single crystal X-ray diffraction. The most stable forms were further characterized by powder diffraction, thermoanalytical (TG/DTA, DSC and thermomicroscopy) and spectroscopic (IR, Raman, ^{13}C CP/MAS NMR) methods.

Introduction

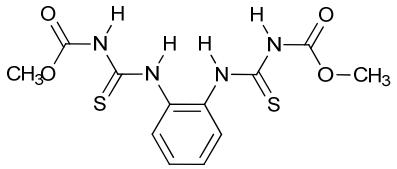
The growing field of crystal engineering deals with designing and synthesizing molecular solid state structures with desired properties.[1] One approach to the subject is using supramolecular synthons[2] composed of molecular fragments and the interactions between them to approximate the possible structural outcome of a crystal.

Polymorphism[3], the ability of a compound to crystallize in more than one distinct crystal form, can be seen as a challenge in crystal engineering, but also as a means to investigate the principles of crystal formation as nature does it. In addition to polymorphs, a number of solvate forms with solvent molecules included in the crystal lattice are commonly formed with the solvent of crystallization.[4] These can further complicate the crystallization of compounds, but can also resolve some unanswered questions and be, for instance, routes to other crystal forms, not easily reached otherwise.[5] The solvent molecules in the crystal structure may either be included to decrease void space in the crystal or be for example hydrogen bonded to the molecules of the compound to better satisfy the possible intermolecular interactions.[6] The occurance of polymorphs and solvates is especially high amongst molecules with flexible torsions and several low energy conformers.[7]

The literature reflects the importance of polymorphism in pharmaceutical substances.[3] The basic questions in agrochemical actives[8] are essentially the same; how many forms can be found and what are properties and thermodynamical relationships of the forms.

We carried out conventional solvent screening investigating the polymorphism of a pesticide active, thiophanate-methyl (TM) (Scheme 1), dimethyl 4,4'-(o-phenylene)bis(3-thioallophanate), which is relatively flexible and capable of forming multiple hydrogen bonds as well as aromatic interactions. The motivation was to investigate whether the variation in melting points reported in the literature (135ºC to 200ºC[9]) is due to the existance of different polymorphs of TM, and on the other hand whether these forms exhibit varying hydrogen bonding arrangements. Recently, multi component crystals, co-crystals, of TM have been reported with different agrochemical actives.[10]

TM is a fungicide and wound protectant and has been used, for example, in protecting citrus fruits against post harvest decay in packing houses.[11] TM belongs to a group of fungicides that transform into benzimidazoles during use with TM specifically transforming into carbendazim.[11,12] Benzimidazoles work by impairing microtubule growth in fungal cells, which consequently prevents correct cell division, as microtubules are needed in forming the spindle that guides the movement of chromosomes during cell division.[13]



Scheme 1 The molecular structure of TM.

Experimental

Materials. TM of 99.8% purity from BASF, distilled water and solvents of analytical purity (min 99%) were used in the crystallization experiments.

Crystallizations. The used solvents included water, acetone, acetonitrile (MeCN), THF, methanol (MeOH), ethanol (EtOH), chloroform, dichloromethane (DCM), 1,2-dichloroethane (1,2-DCE), dioxane, pyridine, 1,2-dichlorobenzene (1,2-DCB), benzene, cyclohexanone, DMSO, dimethylacetamide (DMA), methyl isobutyl ketone and 1,2-propanediol. Amounts of 0.5 to 1.0 g of TM were dissolved in 15 to 100 ml of solvent with the help of an ultrasonic water bath (~40°C). If the entire sample did not dissolve, solutions were filtered through a Witeg Por.2 glass filter. The solutions

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were allowed to evaporate at RT until crystals formed. The crystallizations from acetonitrile, DMA and methyl isobutyl ketone produced form I, while all other crystallizations produced solvates. Form II was acquired by fast crystallization from acetone under reduced pressure and a single crystal was acquired from a 1:1 mixture of acetonitrile and water. Slow cooling crystallizations produced the same results.

Thermomicroscopy. The behavior of crystals during heating was studied under polarized light with a Mettler FP82HT hot stage connected to a Mettler FP90 central processor with an Olympus BH-2 microscope. The primary heating rate used was 10°C/min from 30°C to melting/decomposition of the sample at around 170°C.

TG/DTA. Thermogravimetric/differential thermal analyses were carried out with a Mettler Toledo TGA/SDTA 851 using Al_2O_3 as reference. The samples (8-22 mg) were placed in platinum sample pans for measurement with a temperature program from 30 to 605°C at 10°C/min and N_2 gas flow.

DSC. Differential scanning calorimetric determinations were made on a Mettler Toledo DSC 823e with TS0801RO Sample Robot and TS08006C1 Gas Control. The measurements of form I and form II were done with three different heating rates (5, 10 and 20 °C/min) from 30 to 185°C using aluminum crucibles with pinholes.

Single crystal X-ray diffraction. X-ray diffraction data was collected graphite-monochromated CuKα radiation (λ = 1.54178 Å). The data for TM form I, the methanol, ethanol, DCM, 1,2-DCE, cyclohexanone, DMSO, THF, dioxane, pyridine, 1,2-DCB and benzene solvates was collected at 103 K on a Bruker AXS CCD Detector. The data for TM form II, the chloroform and acetone solvate and the acetonitrile solvate mono hydrate was collected with a Nonius Kappa CCD diffractometer with Apex II detector at 173 K. The structures were solved with direct methods, refined, and expanded by using Fourier techniques with the SHELX-97 software package[14]. Absorption correction was performed with SADABS[15] or Denzo-SMN v0.97.638[16]. Hydrogen atoms were placed in idealized positions (C-H hydrogens) or found from the electron density map (most N-H hydrogens) and included in structure factor calculations. The N-H distances of the hydrogen bonding hydrogens were restrained to 0.91 Å to give the best fit to the X-ray data and to ensure a stable refinement. The WinGX program system[17] and the Shelxtl program package[18] were used. Residual electron density in the DMSO solvate that could be assigned to severely disordered DMSO molecules was removed with the program SQUEEZE[19]. The quality of the ethanol solvate structure solution is poor and thus only preliminary data is given. The methanol in the methanol solvate is disordered over two postions and could only be refined isotropically without hydrogen atoms. The poor quality of several of the structures is due to insufficient data collection as the structures were measured for industrial purposes. Pictures of the structures were drawn with Mercury[20]. Crystal data and collection parameters of the structures are presented in Tables 1 and 2.

PXRD. Powder X-ray diffraction patterns were measured with a Siemens D5000 X-ray diffractometer with a Cu anode (λ = 1.5406 Å; 45 kV, 25 mA). The measurement temperature was 25°C (RT) and a 2θ-angle range of 5–35° and a step resolution of 0.020° was used with a step time of 4.5 s.

^{13}C CP/MAS NMR. The ^{13}C CP/MAS NMR spectra were measured with a Bruker Avance 400 FT NMR spectrometer with a dual 4 mm CP/MAS probehead. The sample was packed in a 4 mm diameter ZrO_2 rotor, which was spun at 10 KHz rate at 296 or 373 K. Contact time for CP was 4 ms, pulse interval 4 s, time domain 2 K, which was zero filled to 8 K in frequency domain. Exponential window function with 5 Hz line broadening was used. 20 000 scans were acquired.

IR and Raman spectroscopy. The IR spectra were measured from KBr tablets on a Thermo Nicolet Nexus 470 IR spectrometer with a DTGS KBr detector. The Raman spectra were measured with a Nicolet 950 FT-Raman spectrometer.

Isothermal microcalorimetry. The dissolution energy of form I and form II was measured on a Thermometric Precision Solution Calorimeter at 25°C with 100 ml of DMSO and 200 mg of TM.

Calculation of gasphase conformers. The conformer screening was performed by a hierarchical procedure. First all possible combinations of dihedral angles were generated to define a first set of 2916 structures. For these structures molecular energies were calculated using the Dreiding force field[21] in combination with the charge equilibration method[22] (charges determined for the initial starting structure were kept fixed). All structures within the first 10000 kcal/mol were extracted and checked for redundancies, which resulted in an intermediate set of 1716 structures. This first part was carried out with tools in the Cerius^2 program[23]. For the intermediate set of structures geometry optimizations were performed on the density functional theory level using the B-P functional[24] and TZVP basis sets[25] in the RI approximation[26]. After removal of redundant structures, 215 distinct conformers were left, which were verified as energy minima by analytical second derivatives of the energy with respect to nuclear positions. The final ranking of conformers was done based on second-order Møller-Plesset perturbation theory (MP2) energy calculations in the RI approximation[27] using TZVPP basis sets[28]. The DFT and MP2 calculations were done with the Turbomole program package[29].

Results and discussion

Polymorphs

Two polymorphs of TM were found and characterized. Form I, of which the original commercially available sample was composed of, crystallized from acetonitrile solution (also from DMA, methyl isobutyl ketone and 1,2-propanediol solutions) and form II, or a mixture of form I and form II, was acquired mostly by desolvation of the found solvates. Pure powdered samples of form II were obtained by reduced pressure evaporation from warm acetone solutions of TM followed by heating at 80°C in a vacuum oven for one hour. Form II was also found to crystallize from acetonitrile:water (1:1, V:V) solution, though not consistently. The next paragraphs describe the crystal structures of both polymorphs. The differences in the conformations of TM are discussed later in the chapter "conformations".

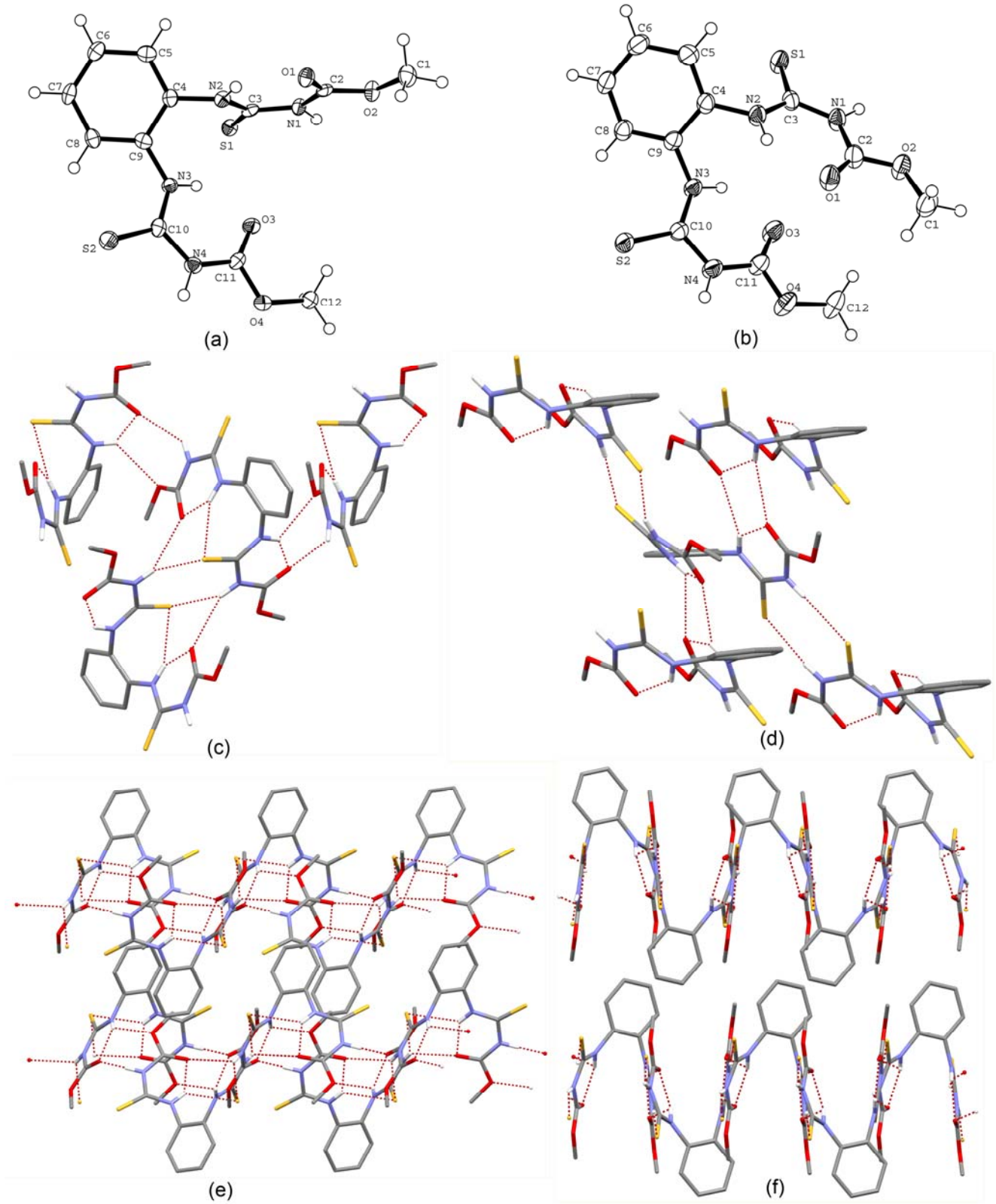

Fig. 1 Ortep plots of (a) form I and (b) form II with the numbering of the atoms in the molecules of TM and hydrogen bonding of TM molecules in (c) form I and (d) form II, and two-dimensional sheets TM molecules viewed from the side in (e) form I and (f) form II. Non-hydrogen bonding hydrogens are omitted for clarity from (c)-(f).

Crystal structure of form I

Block crystals of form I crystallized from acetonitrile solution in the monoclinic space group $P2_1/n$ with one TM molecule in the asymmetric unit (Fig. 1a). In the crystal structure one molecule of TM is hydrogen bonded with 8 hydrogen bonds in all to three adjacent molecules of TM. In addition, there are

three intramolecular hydrogen bonds of which one (N-H•••S=C bond) joins the two arms, i.e. the two functional groups on the benzene ring of the molecule, and the other two (N-H•••O=C bonds) are within the arms (Fig. 1c).

Two types of inter-molecular hydrogen bond arrangements are found in the structure (bonding parameters in ESI). The first is composed of one N-H•••O=C bond and one N-H•••O-C hydrogen bond and causes infinite chains of TM (the top three TM molecules in Fig. 1c). These chains are then connected by hydrogen bonds to parallel chains with a hand-in-hand arrangement that binds a pair of molecules together. This pairing arrangement (the bottom and central molecule in Fig. 1c) consists of intra- and intermolecular bifurcated N-H•••S=C and N-H•••O=C hydrogen bonds. With this arrangement, every other molecule in the infinite chains is connected to one adjacent chain and every other molecule to another adjacent chain. The framework of connected chains produces infinite two-dimensional sheets (Fig. 1e). Aromatic and methyl groups point outward from the sheets making hydrophobic layers that facilitate the stacking of the sheets.

Crystal structure of form II

Block crystals of form II were found to crystallize from a acetonitrile:water (1:1) solution in the monoclinic space group $P2_1/c$ with one molecule of TM in the asymmetric unit (Fig. 1b). In this structure one TM molecule is hydrogen bonded with 8 hydrogen bonds in all to four adjacent TM molecules (Fig. 1d). There is also intramolecular N-H•••O=C hydrogen

Table 1 Crystal data and collection parameters for form I and form II

	Form I	**Form II**
Formula	$C_{12}H_{14}N_4O_4S_2$	$C_{12}H_{14}N_4O_4S_2$
M	342.39	342.39
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (Å)	10.7149(5)	8.946(2)
b (Å)	11.8405(5)	20.052(4)
c (Å)	15.6861(6)	8.998(2)
β (deg)	132.593(2)	107.51(3)
V (Å^3)	1465.1(2)	1539.3(5)
Z	4	4
ρ_{calc} (g/cm^3)	1.552	1.477
Meas reflns	9507	4338
Indp reflns	1744	2653
R_{int}	0.0572	0.0449
R_1 [I>2σ(I)]	0.0402	0.0424
wR_2 [I>2σ(I)]	0.1128	0.1119
GooF	1.187	1.055

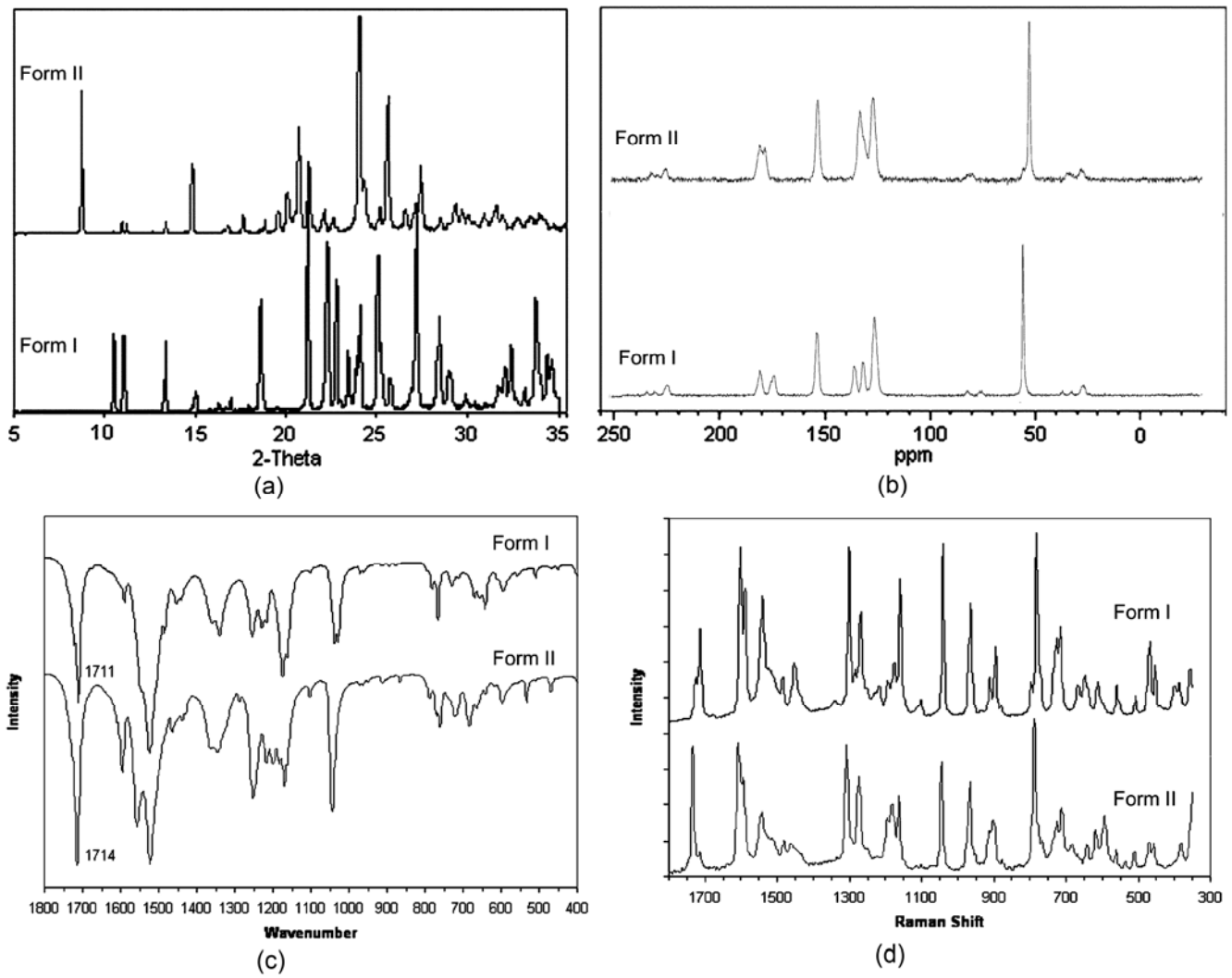

Fig. 2 (a) PXRD patterns (b) ^{13}C CP/MAS NMR spectra, (c) IR and (d) Raman spectra of forms I and II.

bonding within the arms of the molecule.

The TM molecules are connected with two different hydrogen bonding arrangements – one with two N-H•••S=C and one with two N-H•••O=C hydrogen bonds. These arrangements produce infinite two dimensonal sheets of TM molecules (Fig. 1f) that then stack up on each other like those in form I with hydrophobic interactions between the methyl and benzene groups.

Further characterization

The polymorphs were also characterized with PXRD, DSC, TG/DTA, thermomicroscopy, CP/MAS NMR, IR and Raman methods. In the DSCs (ESI) of both forms decomposition started at around 165°C with peak maxima at 174.2°C and 175.9°C for form I and form II, respectively. In the DSC of form I there is additionally a very small endothermic peak at around 115°C, which showed up at all heating rates and is possibly explained by impurities as at that temperature there is no change observed with the thermomicroscope with which form I and fom II could not be distinguished. The TG/DTA (ESI) curves of the two polymorphs were also practically indistinguishable.

The PXRD patterns (Fig. 2a) of the two polymorphs can be clearly distinguished. PXRD patterns were thus used for form identification in further experiments. (Comparisons between experimental and calculated PXRD patterns in ESI).

Forms I and II can also be distinguished from their ^{13}C CP/MAS NMR spectra (Fig. 2b). The methyl group peaks are at 55.1 ppm for form I and 52.2 ppm for form II with a small peak at 55.0 ppm, indicating that the methyl groups are in somewhat different environments in the two forms. The peaks of the ester carbon atoms are at 153.2 ppm and 153.1 ppm for form I and form II, respectively, and thus are in very similar environments.The benzene carbon peaks are different for the two forms and point to 3 types of environments for form I and two types of environments for form II. By comparing the chemical shifts of the corresponding C=S carbon atoms, it can be concluded that the C=S carbons with peaks at around 180 ppm are in more similar surroundings in form II than in form I

Table 2 Crystal data and collection parameters for the solvate crystal forms of TM

	MeCN/H_2O[a]	**DCM**	**1,2-DCE**	**Methanol[a]**	**Ethanol[b]**	**Acetone**	**Cyclohexanone**
Formula	$3C_{12}H_{14}N_4O_4S_2$ •$2.5C_2H_3N$•H_2O	$C_{12}H_{14}N_4O_4S_2$ •CH_2Cl_2	$C_{12}H_{14}N_4O_4S_2$ •$C_2H_4Cl_2$	$2C_{12}H_{14}N_4O_4S_2$ •CH_3OH	$2C_{12}H_{14}N_4O_4S_2$ •CH_3CH_2OH	$2C_{12}H_{14}N_4O_4S_2$ •$(CH_3)_2CO$	$2C_{12}H_{14}N_4O_4S_2$ •$C_6H_{10}O$
M	1147.83	427.32	441.34	719.83	730.85	742.86	782.92
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic	Triclinic	Triclinic	Triclinic
Space group	P-1	P-1	P-1	P-1	P-1	P-1	P-1
a (Å)	10.641(2)	9.313(6)	9.313(2)	10.016(3)	9.842(2)	10.206(2)	11.277(3)
b (Å)	13.751(3)	10.145(6)	10.150(2)	11.430(3)	11.370(2)	11.153(2)	17.368(4)
c (Å)	20.181(4)	10.777(7)	10.735(2)	15.904(5)	15.988(3)	17.062(3)	19.902(5)
α (deg)	74.62(3)	83.04(4)	82.06(2)	101.73(1)	78.99(1)	76.69(3)	92.21(2)
β (deg)	85.49(3)	80.00(4)	79.40(2)	90.33(1)	89.34(1)	86.07(3)	103.76(2)
γ (deg)	77.97(3)	80.12(4)	79.41(2)	107.692(9)	72.15(2)	72.46(3)	100.77(1)
V (Å^3)	2784(1)	984(2)	974.7(4)	1694.0(9)	1669.5(5)	1802.0(6)	3705(2)
Z	2	2	2	2	2	2	4
ρ_{calc} (g/cm^3)	1.369	1.443	1.504	1.405	1.454	1.369	1.404
Meas reflns	12985	3274	8006	7891	9780	8844	28524
Indp reflns	9441	1992	2410	3543	3869	6210	9162
R_{int}	0.0832	0.0490	0.0450	0.0606	0.0660	0.1118	0.0473
R_1 [I>2σ(I)]	0.0719	0.0680	0.0358	0.0726	0.1717	0.0487	0.0411
wR_2 [I>2σ(I)]	0.1748	0.1767	0.0910	0.1975	0.4942	0.1271	0.0938
GooF	1.062	1.037	1.059	1.104	2.166	1.022	1.038

	DMSO[c]	**Chloroform**	**THF**	**Dioxane**	**Pyridine**	**1,2-DCB**	**Benzene**
Formula	$C_{12}H_{14}N_4O_4S_2$ •C_2H_6OS	$C_{12}H_{14}N_4O_4S_2$ •$CHCl_3$	$C_{12}H_{14}N_4O_4S_2$ •C_4H_8O	$C_{12}H_{14}N_4O_4S_2$ •$C_4H_8O_2$	$C_{12}H_{14}N_4O_4S_2$ •C_5H_5N	$C_{12}H_{14}N_4O_4S_2$ •$C_6H_4Cl_2$	$C_{12}H_{14}N_4O_4S_2$ •C_6H_6
M	420.52	461.76	414.52	430.50	421.49	489.38	420.50
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic	Triclinic	Triclinic	Triclinic
Space group	C2/c	P-1	P-1	C2/c	P-1	P-1	P-1
a (Å)	26.52(2)	10.626(2)	10.546(2)	21.97(1)	8.244(1)	7.9951(7)	8.4106(8)
b (Å)	10.321(5)	14.706(3)	14.470(3)	11.428(5)	10.690(2)	9.5484(9)	9.9524(9)
c (Å)	17.43(1)	14.739(3)	14.592(2)	17.147(7)	12.493(2)	14.702(2)	12.952(2)
α (deg)	90	63.51(3)	65.317(8)	90	67.892(5)	81.910(4)	107.946(4)
β (deg)	94.66(3)	77.34(3)	77.66(1)	111.24(2)	81.442(6)	84.862(4)	101.732(5)
γ (deg)	90	74.82(3)	76.29(1)	90	74.153(5)	73.646(4)	96.983(4)
V (Å^3)	4755(5)	1975.6(7)	1948.8(6)	4014(3)	979.9(2)	1064.7(2)	991.0(2)
Z	8	4	4	8	2	2	2
ρ_{calc} (g/cm^3)	1.175	1.552	1.4013	1.425	1.429	1.526	1.409
Meas reflns	12637	10630	9286	7583	7870	7159	8528
Indp reflns	3184	6828	4514	2484	2437	2645	2494
R_{int}	0.1367	0.0679	0.0407	0.0475	0.0321	0.0323	0.0313
R_1 [I>2σ(I)]	0.0899	0.0557	0.0526	0.0679	0.0434	0.0459	0.0373
wR_2 [I>2σ(I)]	0.2145	0.1358	0.1494	0.1866	0.1082	0.1127	0.0889
GooF	0.988	1.027	1.123	1.079	1.167	1.201	1.106

[a] The H_2O/MeOH hydrogen atoms could not be accurately placed, [b] Preliminary data, [c] Due to the removal of a disordered DMSO molecule by Squeeze[17] the chemical formula, molecular weight and density are not accurate.

since the peak separation is bigger in the spectrum of form I. From the crystal structures one can see the reason for this as in form I only one sulfur seems to be involved in hydrogen bonding and in form II both sulfurs are hydrogen bonded. Also because in form II both C=S carbon chemical shifts are deshielded in comparison to those in form I, one can conclude from the CP/MAS NMR spectrum that in form II both C=S groups are hydrogen bonded.[30]

There are differences in the IR and Raman spectra (Fig. 2c and d) of the two forms, but these were not investigated further due to PXRD being such a good method to differentiate the two forms. The IR rule[31] can be used to determine the stability order of polymorphs. The first absorption band of carbonyl oxygen atoms in the fingerprint region for form I is at 1711 cm^{-1} and for form II at 1714 cm^{-1}. The difference is small and inconsistent with other data as it indicates form II being more stable. This difference of 3 cm^{-1} could also indicate greater involvement of the carbonyl oxygen atoms of form I in intermolecular interactions.

Transformation and stability

According to thermal analysis the relationship between the two polymorphs is monotropic, as no endothermic (or exothermic) transition is observed for either form. Temperature variable ^{13}C CP/MAS NMR (form II, RT to 100°C) and PXRD (form I, RT to 130°C) analyses also indicate no transformations. However, no melting temperature could be determined and no heat-of-fusion could be measured because of the decomposition of TM and thus the heat-of-fusion rule[31] could not be used to back up our interpretation.

Form I has a calculated density of 1.51 g/cm³ and form II 1.46 g/cm³. According to the density rule[31] the denser polymorph, in this case form I, is more stable at absolute zero. As the relationship between the polymorphs is monotropic, form I is also more stable at all temperatures. The energies of dissolution, measured by solution microcalorimetry, were -4.011 kJ/mol for form I and -6.724 kJ/mol for form II. According to the results, form I is approximately 2.7 kJ/mol lower in energy than form II. Form II also converts to form I when mixed in a suspension of water and in water-glycerol mixtures, giving further evidence of the stability of form I.

The solution-mediated transformation from form I to form II occurred faster at elevated temperatures (80°C) than at room temperature indicating form I to be more stable also at higher temperatures.

Solvates

Fourteen solvates of TM (acetonitrile/water, methanol, ethanol, acetone, DMSO, cyclohexanone, dichloromethane, 1,2-dichloroethane, dioxane, pyridine, 1,2-dichlorobenzene, THF, chloroform and benzene) were encountered during the investigations (Table 3). All but the acetonitrile solvate monohydrate crystallized quite consistently from solutions of the corresponding solvents. Crystal structures of all the found solvates were determined. The hydrogen bonding networks and packing of the solvates is complex, as can be expected by the various hydrogen bonding possibilities and the vast amount of low energy conformers offered by TM. We do not feel that a detailed analysis is necessary here. However, we try to bring up some common features and categorize the structures where applicable.

Stability and desolvation behavior

When taken out of solution, the solvates desolvate at temperatures from room temperature (RT) to around 130°C, as determined by thermomicroscopy (HS) and TG/DTA (Table 3). Most of the solvates also desolvate quite rapidly at room temperature when left out of solution, though the methanol and ethanol solvates seem to be rather stable and stay solvated for weeks even when out of solution. Upon desolvation (in a vacuum oven at temperatures of 80-130°C depending on the desolvation temperature of the solvate) the tested solvates produce form II or a mixture of form I and form II, as determined with PXRD. According to the experiments, a correlation could not be recognized between the structure of the solvated or the desolvation temperature and the preferred desolvation product, even though the acetone, DCM, THF and chloroform solvates, which desolvate even at room temperature, appear to produce preferentially only form II. The reason for the emergence of mixtures may be solvent-mediated transformation occurring when the solvent does not leave from around the crystals as they desolvate.

Hand-in-hand pairs

Table 3 Habits, ratios of TM to solvent from TGA data, desolvation temperatures and the forms after desolvation of the found solvates

Solvate	Habit	Ratio	Desolvation T (°C)		After desolvation	Solvent BP
			HS	TGA		
DCM	Blocks	1:1	<75	-	Form II	39.8
1,2-DCE	Blocks	1:1	72	73	Form II & Form I	83.5
Acetonitrile/water	Needles	1:1 [a]	RT	-	-	82
Methanol	Plates	2:1	131	148	Form II & Form I	64.7
Ethanol	Plates	2:1	130	140	Form I & Form II	78.4
Cyclohexanone	Plates/rods	2:1	109	112	Form I & Form II	155.7
DMSO	Plates/blocks	1:1 (1:2) [b]	71-130	88	Form II & Form I	189
THF	Rods	1:1	<84	76	Form II	66
Dioxane	Blocks	1:1	80	111	Form II & Form I	101.1
Pyridine	Irregular blocks	1:1	85	125	Form II	115.2
1,2-DCB	Blocks	1:1	62	-	Form I & Form II	180.5
Benzene	Blocks/plates	1:1	58	-	-	80.1
Acetone	Plates	2:1	84	83	Form II	56.3
Chloroform	Needles/rods	1:1 (2:1) [c]	<60	63	Form II	61.2

[a] More precisely 3:2.5:1 (TM:MeCN:H_2O) [b] The TM to DMSO ratio of 1:2 from the structure solution disagrees with the TGA result of 1:1 because of overlaps in the TGA due to the high boiling point of DMSO and the comparitatively low desolvation point of the DMSO solvate [c] The TGA result of 2:1 disagrees with that of the structure solution most likely due to partial desolvation before analysis.

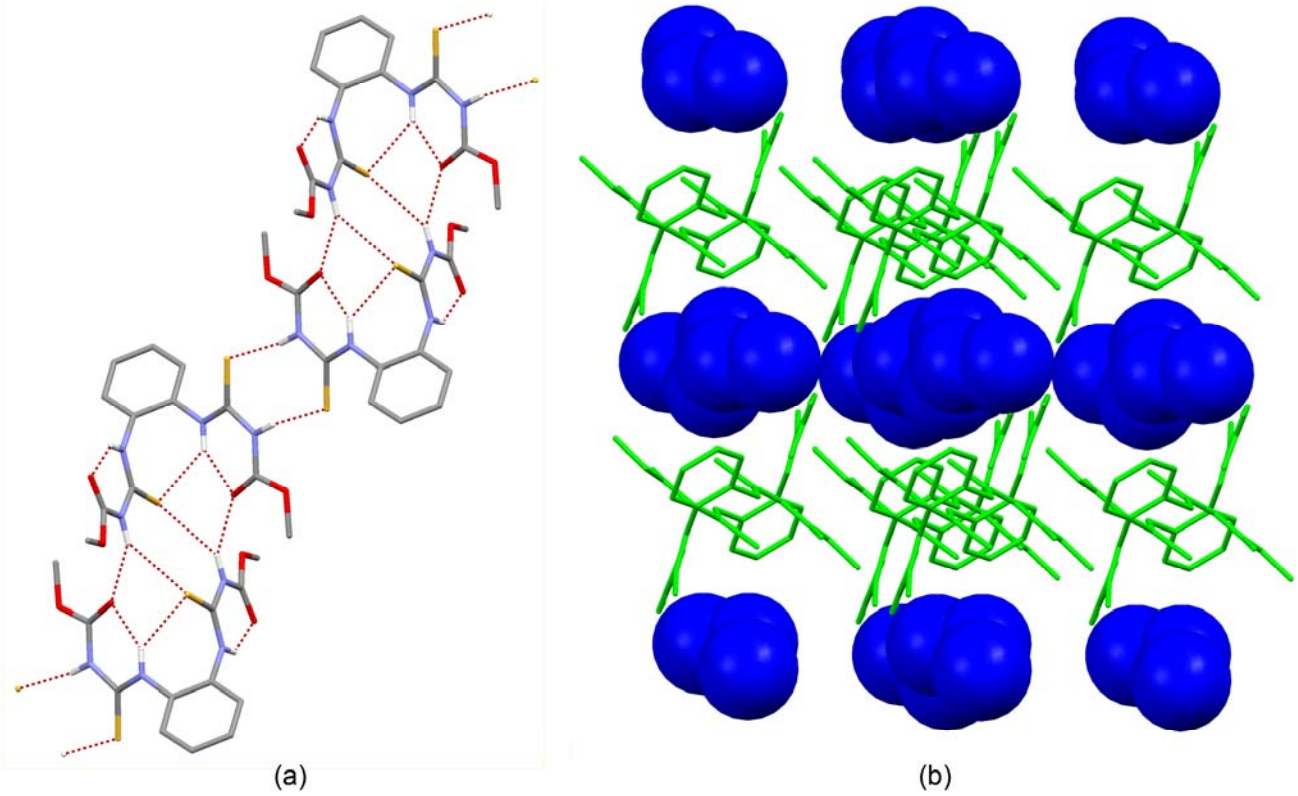

Fig. 3 (a) Hydrogen bonding of TM in the DCM and 1,2-DCE solvates (from the DCM solvate) and (b) solvent channels in the DCM solvate with the DCM molecules in spacefill style. Non H-bonding hydrogens are omitted for clarity.

The dichloromethane and 1,2-dichloroethane solvates are isomorphic and crystallize from the respective solvents by evaporation and cooling crystallization in the triclinic space group P-1 with one molecule of TM and one solvent molecule in the asymmetric unit. The TM molecules arrange in hand-in-hand pairs like the ones in form I. The pairs, however, are connected to each other with two N-H•••S=C hydrogen bonds rather than the N-H•••O-C hydrogen bonds that connect the pairs in form I (Fig. 3a). This arrangement of hydrogen bonds causes 1-dimensional parallel chains of TM molecules.

The solvent molecules are situated in channels between chains of TM molecules (Fig. 3b). The distance between the closest aromatic H atoms and the Cl atoms in the DCM structure is approximately 3.07 Å, which indicates a weak interaction. The C-H hydrogen atoms of the solvent molecules in the DCM structure are also weakly hydrogen bonded to the sulfur atoms of TM with C•••S distances of 3.68 Å and 3.93 Å and angles of 156° and 173°, respectively.

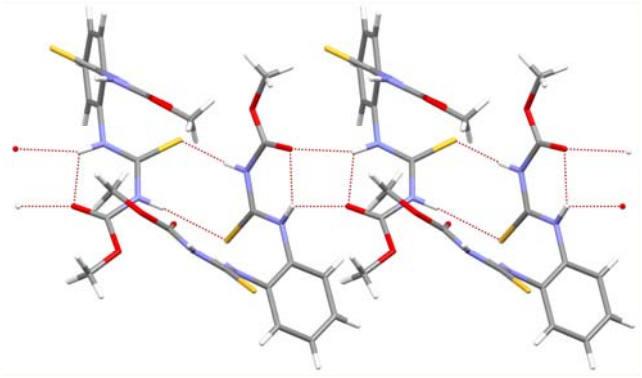

Fig. 4 One-armed chain of TM molecules (from the methanol solvate) connected by N-H•••S=C and N-H•••O=C hydrogen bonds. Non H-bonding hydrogens are omitted for clarity.

One-armed chains

The methanol, ethanol, acetone and THF solvates crystallize in the triclinic space group P-1 with two TM molecules in the asymmetric unit. The cyclohexanone solvate also crystallizes in the spacegroup P-1, but with four TM molecules in the asymmetric unit, whereas the DMSO solvate crystallizes in the monoclinic space group C2/c with one TM molecule in the asymmetric unit. In these solvates the main arrangement of hydrogen bonding is one where the molecules of TM arrange in chains, which include hydrogen bonds mainly to one arm of the molecules (Fig. 4 and ESI). Two types of hydrogen bond arrangements build up these chains, of which one is composed of two N-H•••S=C hydrogen bonds and the other of two N-H•••O=C hydrogen bonds between the molecules.

Though the hydrogen bonding pattern of the chains is the same for all the solvates with one-armed chains, the orientation of the molecules in the chains is different due to the inclusion of different solvent molecules. The methanol, ethanol and acetone solvate structures are nearly isomorphic and the cyclohexanone solvate structure is most similar with them. The THF and DMSO solvate structures are quite different from the rest and each other. The variance in the orientation of TM molecules in the chains is most apparent in the angles of the N-H•••S=C hydrogen bonds (see ESI for hydrogen bonding parameters of all the solvates).

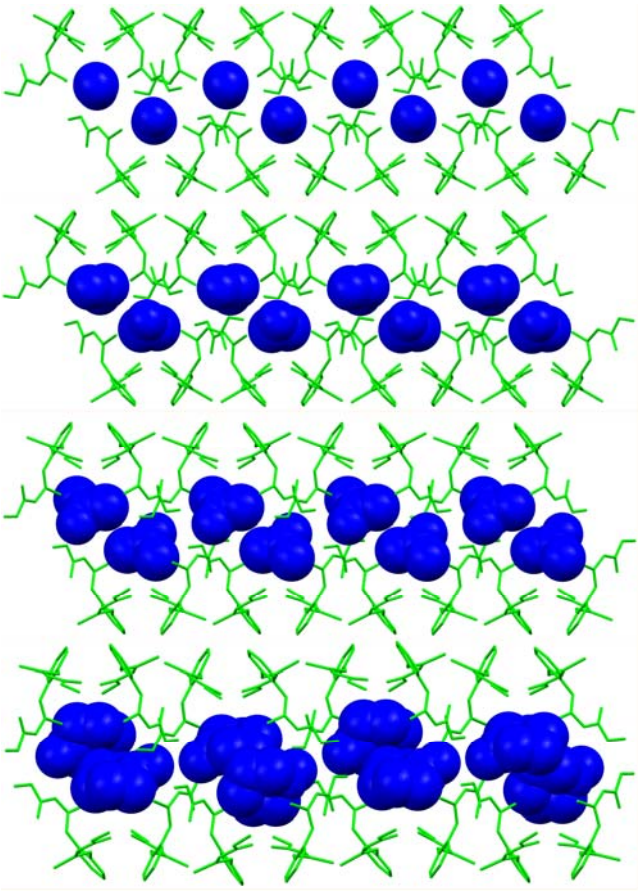

Fig. 5 Two-dimensional sheets in the methanol, ethanol, acetone and cyclohexanone solvates. Non H-bonding hydrogens are omitted for clarity.

The arm of the TM molecules that does not build up the one-armed chains is involved in hydrogen bonding to the solvent molecules and/or in direct hydrogen bonding between adjacent chains (see ESI for pictures). In the methanol and ethanol solvates the chains are connected through two N-H•••S=C hydrogen bonds between TM molecules and through

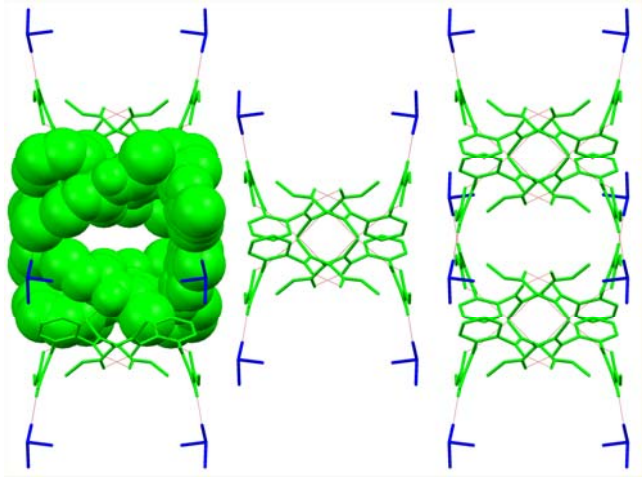

Fig. 7 DMSO solvate from one side showing the role of the ordered DMSO molecules and the channels for disordered DMSO molecules. Non H-bonding hydrogens are omitted for clarity.

hydrogen bonding to the solvent molecules, which act as both a hydrogen bond donor and acceptor. In the acetone and cyclohexanone solvate, the chains are connected with bifurcated hydrogen bonding through the solvent molecules and in the cyclohexanone solvate additionally with N-H•••O-C hydrogen bonds between the TM molecules.

In the methanol, ethanol, acetone and cyclohexanone solvates the connected chains build up two-dimensional sheets composed of solvent molecules in between two layers of TM molecules (Fig. 5). These sheets then stack up on each other, being the cause for the plate-like habit of the crystals.

The THF and chloroform solvates are isomorphic with each other (Fig. 6a and b). The difference between the two is the ability of the THF molecule to form hydrogen bonds with TM and in the chloroform solvate the parallel one-armed chains are connected through hydrogen bonding via an arrangement of two N-H•••S=C hydrogen bonds but in the THF solvate they are not. These two solvates have a 1 to 1 ratio of TM to solvate unlike the other solvates with the same one-armed

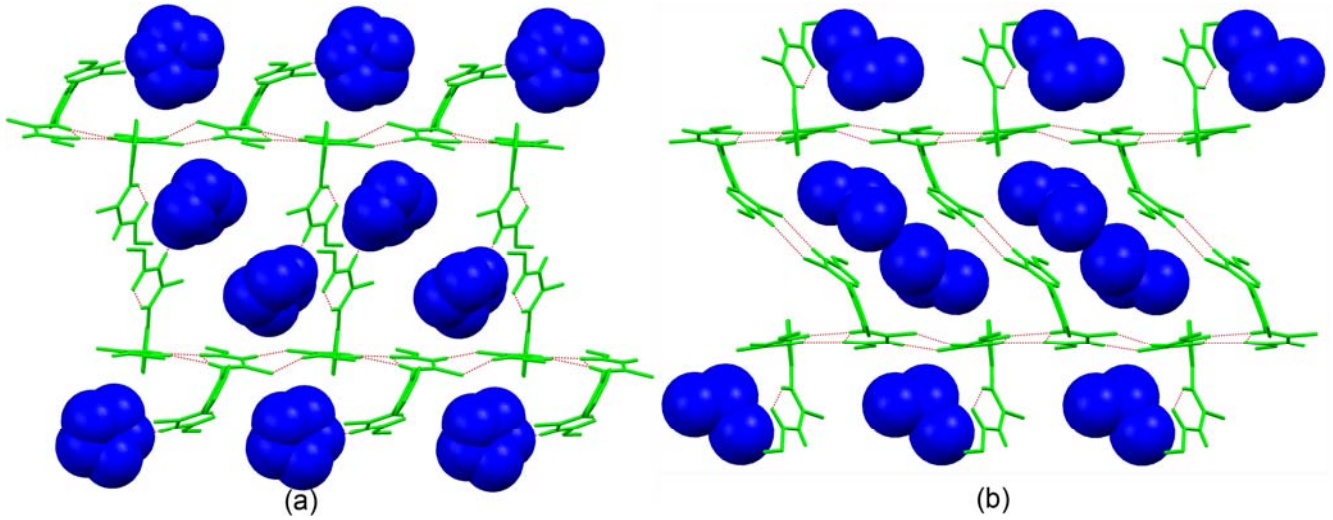

Fig. 6 Parallel packing of chains of the (a) THF solvate and the (b) chloroform solvate with solvent molecules in spacefill style. Non H-bonding hydrogens are omitted for clarity.

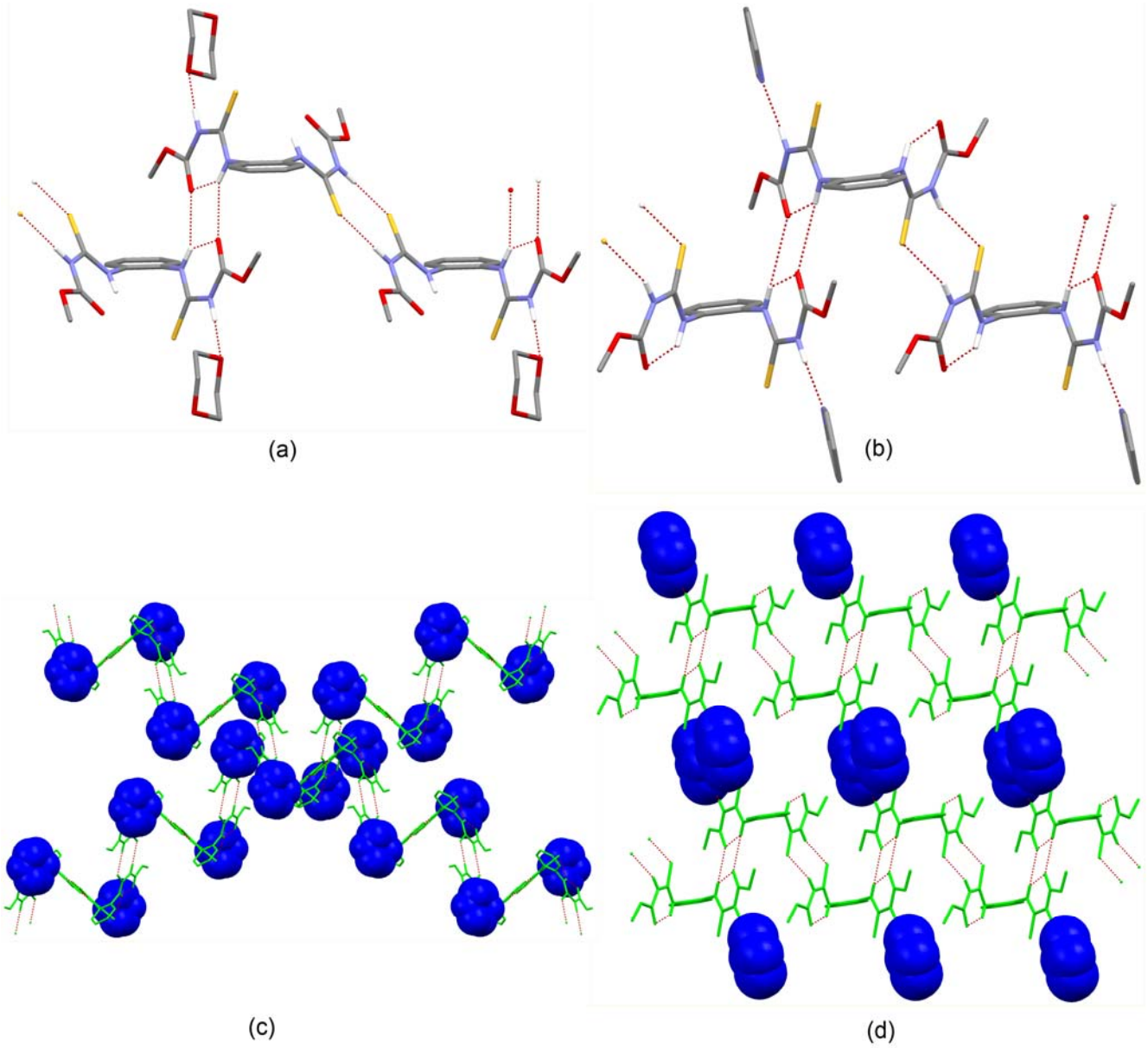

Fig. 8 Two-armed chains of TM molecules from the (a) dioxane and (b) pyridine solvates and (c) crossing chains of the dioxane solvate and (d) parallel chains of the pyridine solvate viewed down the crystallographic a-axis with solvent molecules in spacefill style. Non H-bonding hydrogens are omitted for clarity.

chain hydrogen bonding arrangement of TM molecules.

In the DMSO solvate the one-armed chains, which pack parallel to each other, are not connected through hydrogen bonding. The severely disordered DMSO molecules in the DMSO solvate are placed in cavities that are lined up to form small tubular channels running through the crystal. These channels can be seen between the parallel chains when viewed from the side (Fig. 7). No hydrogen bond donors of the TM molecules point into these cavities and it is likely that the disordered DMSO molecules are merely co-crystallized to fill the empty space. The analysis of the removed electron density supports the hypothesis of having eight disordered DMSO molecules in the unit cell making the TM to solvent ratio 1:2.

Two-armed chains

The dioxane and pyridine solvates crystallize in the monoclinic space group C2/c and the triclinic space group P-1, respectively, but the hydrogen bonding pattern of the TM molecules in these solvates is the same. The molecules of TM build up chains with arrangements of two N-H•••S=C hydrogen bonds and two N-H•••O=C hydrogen bonds involving both the arms of the molecule (Fig. 8a and b). Again as for the one-armed chains, the N-H•••S=C hydrogen bonds show more variability in angles than the N-H•••O=C hydrogen bonds with the hydrogen bonds in the pyridine solvate being somewhat longer than those in the dioxane solvate.

In the pyridine solvate the chains arrange parallel to each other and in the dioxane solvate they cross each other (Fig. 8c and d). In the pyridine solvate the pyridine molecules are located in channels running down the crystallographic a-axis (Fig. 8d). In the dioxane solvate there are no specific channels where the dioxane molecules reside, but they are located

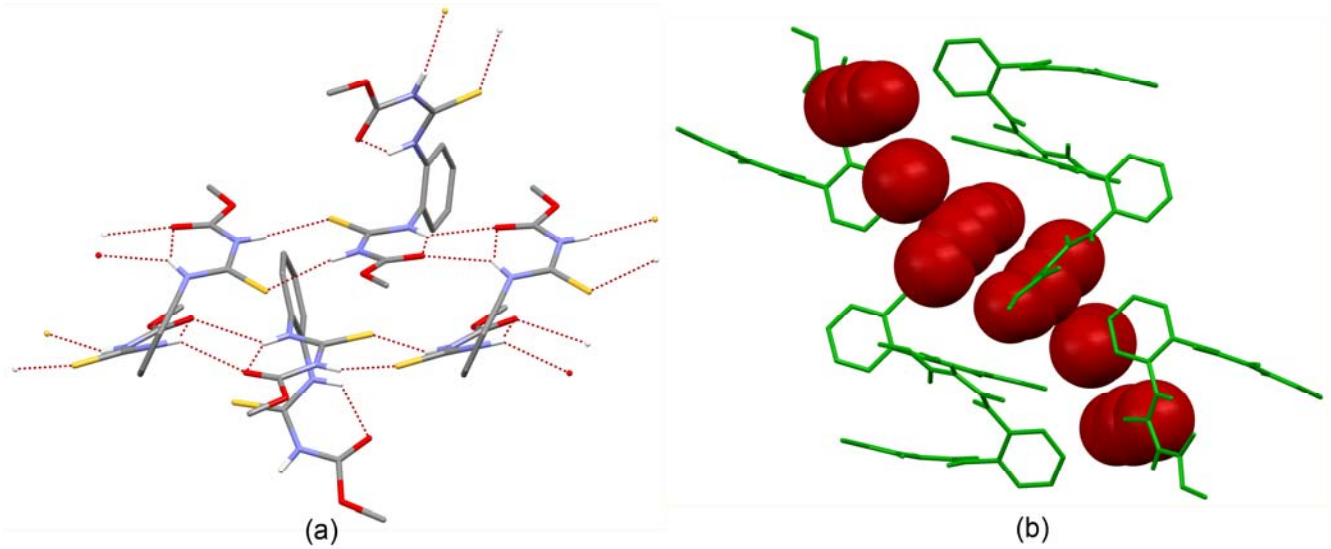

Fig. 9 (a) The hydrogen bonding arrangement and (b) the solvent channels in the MeCN solvate. Non H-bonding hydrogens are omitted for clarity.

pairwise in cavities in the structure.

Acetonitrile solvate mono hydrate

The acetonitrile solvate mono hydrate crystallized from a 1:1 (V:V) acetonitrile:water solution in the triclinic space group P-1 and in addition to acetonitrile there is a molecule of water in the asymmetric unit in addition to three TM molecules, 2 MeCN molecules and one MeCN molecule with a population density of 0.5. No solvate with acetonitrile without water or vice versa could be crystallized despite many attemps.

The hydrogen bonding arrangement is a combination of the arrangements in the one-armed and two-armed chains and mostly similar to that in form II with double chains composed of hydrogen bonding arrangements with two N-H•••S=C or two N-H•••O=C hydrogen bonds (Fig. 9a). The solvent molecules are located in channels (Fig. 9b) and hinder the formation of intact two-dimensional sheets like those in form II. The acetonitrile solvate mono hydrate could, in fact, be a means to the crystallization of form II as they crystallized from the same solution (different flasks).

Aromatic solvate structures

The structures of the aromatic solvates, 1,2-DCB and benzene, are considerably different from those of the other solvates and also from each other. In addition to varying hydrogen bonding (see ESI for hydrogen bonding parameters), the conformation of the molecules of TM is also somewhat different in the structures of the 1,2-DCB and the benzene solvate.

The 1,2-dichlorobenzene solvate crystallizes in the triclinic space group P-1 with one molecule of TM and one molecule

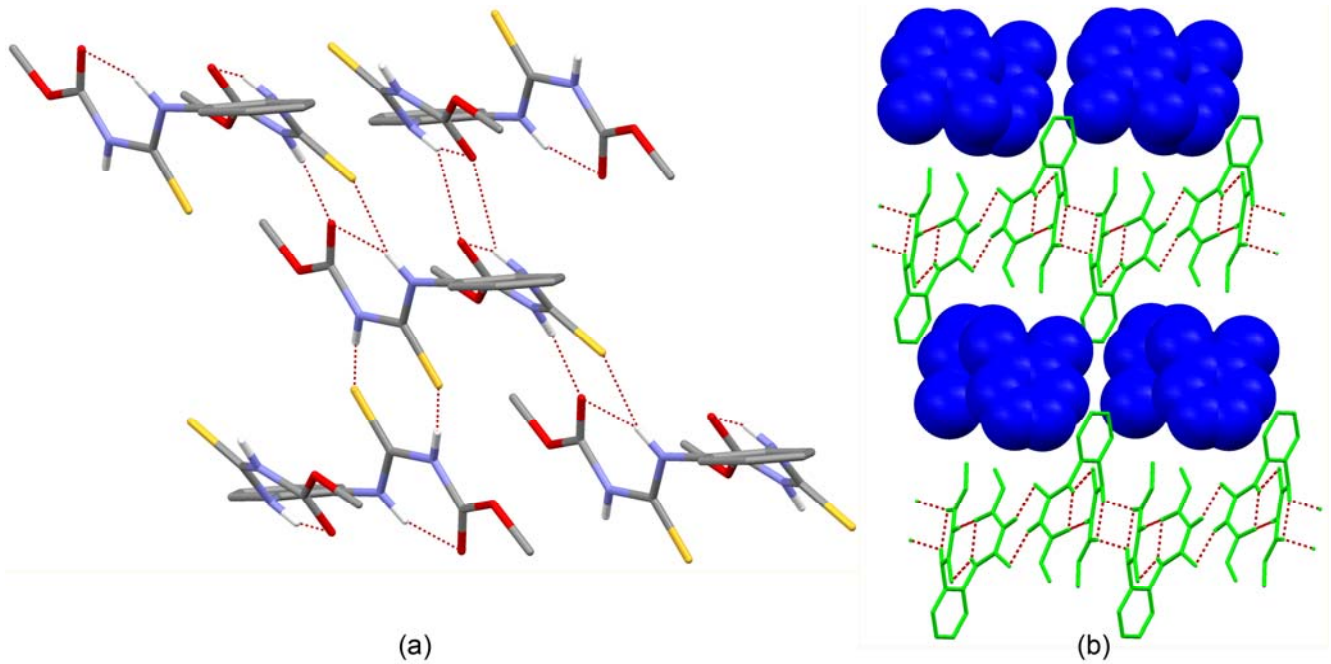

Fig. 10 (a) Hydrogen bonding in the 1,2-DCB solvate and (b) packing of the 1,2-DCB solvate sheets with 1,2-DCB molecules in spacefill style. Non H-bonding hydrogens are omitted for clarity.

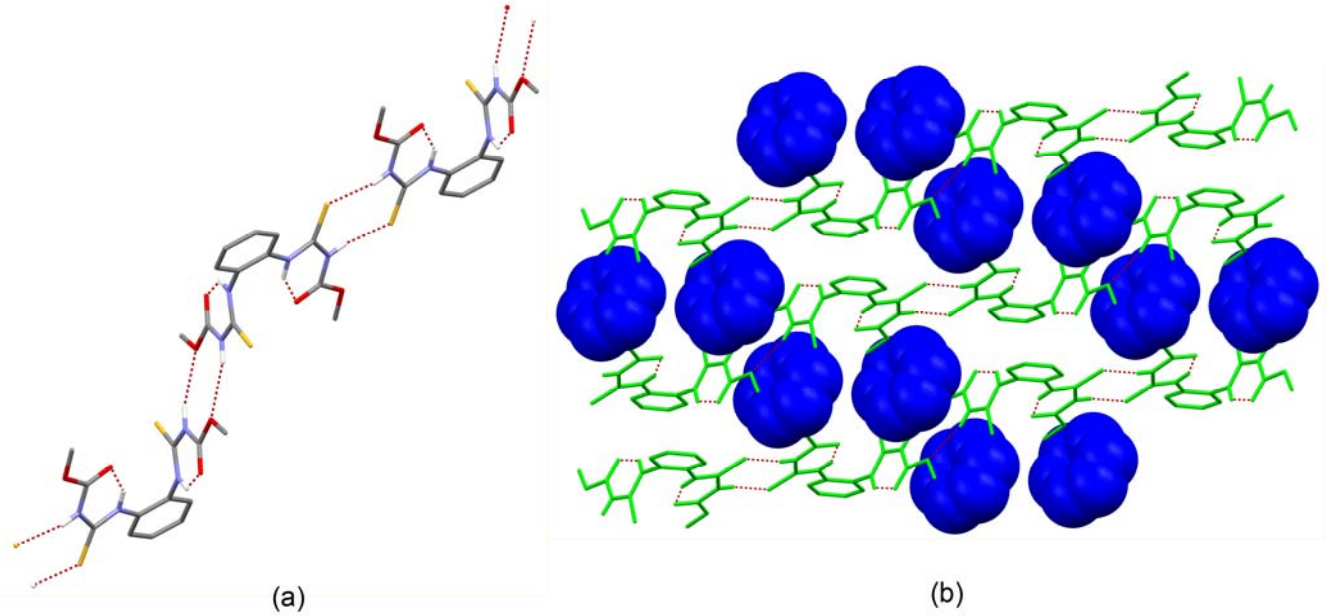

Fig. 11 (a) Chains of TM molecules and (b) the packing of the chains (with benzene molecules in spacefill style) in the benzene solvate. Non H-bonding hydrogens are omitted for clarity.

of solvent in the asymmetric unit. The arrangement of the TM molecules in the 1,2-DCB solvate resembles that in form II except there are three instead of two hydrogen bond arrangements building up the structure and the conformation of the TM molecule is different. One of the hydrogen bonding arrangements consists of two N-H•••S=C hydrogen bonds, another of two N-H•••O=C hydrogen bonds and the third of one N-H•••S=C hydrogen bond and one N-H•••O=C hydrogen bond (Fig. 10a).

The hydrogen bonding arrangements make up two-dimensional sheets of TM that stack up on each other, separated by the 1,2-DCB molecules (Fig. 10b). The benzene and methyl groups of TM protrude to both sides of the sheets, and aromatic interactions and weak C-H•••Cl hydrogen bonds are expected between these groups and the 1,2-DCB molecules.

The hydrogen bonding in the benzene solvate structure is not similar to other structures because of N-H•••O-C hydrogen bonds which are otherwise only found in form I and in the cyclohexanone solvate in combining the chains. A pair of these H•••O-C hydrogen bonds and a pair of N-H•••S=C hydrogen bonds build up chains of TM molecules (Fig. 11a). The distance between the sulfur, that is not hydrogen bonded to an amine hydrogen, and the methyl carbon is 3.732 Å which points toward possible weak C-H•••S=C hydrogen bonding interactions. The chains pack parallel to each other with the benzene molecules in channels running through the structure (Fig. 11b).

Summary of the structures

There are interesting similarities and differences in the hydrogen bonding arrangements and the conformations of the TM molecules in the sixteen described structures. These will be summarized here and the calculated gas phase conformers will also be looked at briefly.

Hydrogen bonding arrangements

The TM molecule has six possible hydrogen bond acceptors (two ester groups with two oxygen acceptors and two sulfur acceptors) and four amine hydrogens as possible hydrogen bond donors. This causes a number of possible intra- and intermolecular hydrogen bonding arrangements, many of which are exhibited in the described structures.

The main hydrogen bonding arrangements seem to be pairs of N-H•••O=C and N-H•••S=C hydrogen bonds, but the hand-in-hand pairing of TM molecules found in form I and the DCM and 1,2-DCE solvates seems to be favorable enough to bring about the formation of the weaker N-H•••O-C hydrogen bond paired to a N-H•••O=C hydrogen bond in the most stable form I, leaving a sulfur acceptor unused. Interestingly, in the benzene solvate pairs of N-H•••O-C hydrogen bonds seem to be favored, leaving the C=O groups to hydrogen bond only intramolecularly and half the sulfur acceptors unused. Mixed pairs of one H•••O=C and one N-H•••S=C hydrogen bond are found only in the 1,2-DCB solvate and form I.

Conformations

The arms of the TM molecules are fairly planar in all structures due to intramolecular N-H•••O=C hydrogen bonds between N2 and O1, and N3 and O3 (the numbering of atoms is in Fig. 1).The conformations of the molecules are thus described by comparing the position of the arms of the molecules in respect to the plane of the benzene ring.

As can be seen in Figure 12 a-d, the two polymorphs, form I (Fig. 12a) and form II (Fig. 12b), represent not only different hydrogen bonding, but also conformational polymorphism and, moreover, different conformers of TM are also observed in the solvate structures. The most remarkable difference in between form I and form II is that, unlike form II, form I has an intermolecular N-H•••S=C hydrogen bond connecting the two arms of the molecule in addition to the above mentioned N-H•••O=C hydrogen bonds within the arms of the molecule. Interestingly, the acetonitrile/water solvate, with Z´=3, has

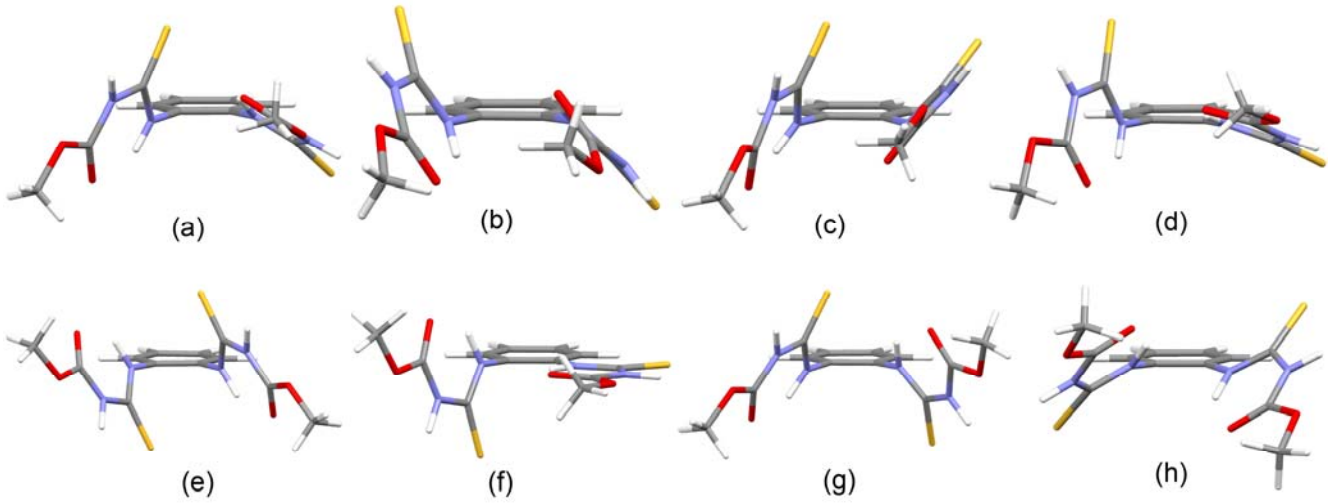

Fig. 12 Conformations of the TM molecules in (a) form I, (b) form II, (c) the 1,2-DCB and (d) benzene solvates and the four calculated gas phase conformers with the lowest energy (e) ΔE = 0 kJ/mol (f) ΔE = 3.22 kJ/mol (g) ΔE = 5.40 kJ/mol (h) ΔE = 7.57 kJ/mol viewed roughly down the plane of the benzene ring.

one of the three independent TM molecules in a confomation like that in form II and the other two more like that in form I, but not close enough as to have an intermolecular N-H•••S=C hydrogen bond (N-H•••S=C distance approximately 3.1 Å in comparison to 2.7 Å in form I).

Calculations of the gas phase conformers of TM were done in order to get insight about the relative energies of the found conformers. Relative to the conformer with the lowest calculated energy, there are six conformers with a ΔE less than 20 kJ/mol and a total of 214 with a ΔE less than 100 kJ/mol. The six lowest energy conformers thus lie in an energy range comparative to one moderately strong hydrogen bond. The four most stable conformers (ΔE less than 8 kJ/mol, Fig.12e-h) all have the intramolecular N-H•••O=C hydrogen bond that is seen in all of the crystal structures. In conformations with higher energy this bond can be changed into a N-H•••O-C hydrogen bond, and in even higher energy conformers an arm of the TM molecules can be twisted into a non-planar conformation with no intra-molecular hydrogen bonding, making these higher energy conformations unlikely in crystals structures.

The conformers observed in the crystal structures have varying torsion angles between the plane of the benzene ring and the arms of the molecules with the gas-phase minimized state and direct comparison is not feasible. For example, the most stable gas phase conformer (Fig. 12e) has no good matches in the determined crystal structures, though one of the TM molecules in the MeCN/H_2O solvate comes close. The second conformer (Fig. 12f) resembles that in the benzene solvate (Fig. 12d). The third gas-phase conformer (Fig. 12g) is quite like that in many of the solvate crystal structures and form I, but most closely resembles the TM molecules in the THF and cyclohexanone solvates. The fourth conformer (Fig. 12h) resembles most closely that in form II of TM (Fig. 12b).

The aromatic solvates have conformations of TM most unlike those in the other structures. In the benzene solvate one arm of the molecule is more in the plane of the benzene ring whereas the other arm is, conversely, less in the plane of the benzene ring than in form I. Further, the conformation of TM in the 1,2-DCB solvate (with sulfur atoms on the same side of the aromatic plane) was not found among the gas phase conformers. In this structure the planes of the arms of the TM molecules are almost parallel to each other, which is also the case in form II, and enables the formation of the similar hydrogen bonded sheet arrangements in the structures.

A lattice energy analysis and a constrained energy optimization of the observed crystal structure conformers is left out of this study as the authors do not expect that such an analysis would bring more essential information. It is, however, clear that the variability of the conformations of TM in the solved crystal structures is paralleled by a number of gas phase conformers with small energy differences and this flexibility probably accounts for the large number of solvates of TM.

Conclusions

TM was found out to exists in two polymorphic forms which have very similar melting points. The original and known form I is the thermodynamically most stable form, which is monotropically related to Form II. Form II can be accessed via desolvation of various different solvate forms.

The discovery of a series of fourteen solvates and the structure determination of these via single crystal X-ray measurement is the highlight of this work. Solvent molecules capable of forming hydrogen bonds (acting either as hydrogen bond acceptors or both acceptor and donor) presented the majority, but also other, such as 1,2-dichlorobenzene and benzene were among solvate forming solvents. The isostructural methanol and ethanol solvates, with desolvation points around 140°C, were remarkably stable against desolvation, whereas the non-hydrogen bonded solvates solvated already at ambient conditions.

The single crystal structures reported here represent a variety of interaction possibilities of TM varying from hydrogen

bonding to aromatic and lipophilic interactions. No clear patterns in packing or formation could be drawn from the structures. It is however noteworthy that TM has a large amount of low energy conformers and several possibilities of forming hydrogen bonds. These two facts can as tradeoff, lead to new hydrogen bonding and close packing modes and can reduce the total energy difference between alternate crystal structures. The search in the CSD by van de Streek[32] shows that there are only a few compounds, many of which are not organic neutral compounds of the size of TM, with ten or more solvate structures reported. It is very likely that, similar to sulfathiazole with its over one hundred solvates[33], several new solvates and also co-crystals with a variety of different functional groups could be found for TM.

As shown in this paper, crystallographical methods play a key role in studying polymorphism and solid state structures. However, also all the used spectroscopical methods (^{13}C CP/MAS NMR, IR and Raman) are usefull in identifying the polymorphic forms of TM from each other and can be valuable in cases where crystallographical methods are not available or can not be applied. Thermoanalytical methods are also especially helpful in determining the stability of a new modification and resolving whether it is a solvate or not.

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