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Supramolecular Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713649759>

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To cite this Article Caira, Mino R. and Mohamed, Riana(1993) 'Inclusion compounds with the drug 5-Methoxysulphadiazine: Structures, thermodynamics of decomposition and relationship to polymorphism of the sulphonamide', *Supramolecular Chemistry*, 2: 2, 201 – 207

To link to this Article: DOI: 10.1080/10610279308038317

URL: <http://dx.doi.org/10.1080/10610279308038317>

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Inclusion compounds with the drug 5-Methoxysulphadiazine: Structures, thermodynamics of decomposition and relationship to polymorphism of the sulphonamide

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(Received July 30, 1992)

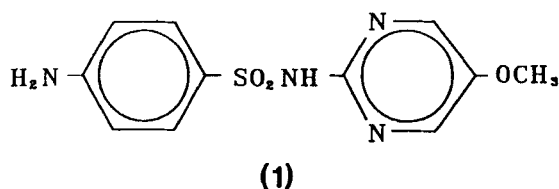
The structures and thermal decompositions of the solvates of 5-methoxysulphadiazine with dioxane, chloroform and tetrahydrofuran have been investigated by X-ray analysis, differential scanning calorimetry and thermogravimetry. These species are clathrates with 1:1 host-guest stoichiometry crystallizing in space group $P2_1/c$ with very similar unit cell parameters. Their structures are based on a common isostructural host framework in which the guest molecules occupy channels with the narrowest constriction being 2 Å. The unusual stability of these species and their decomposition to a common polymorph (Form I) of 5-methoxysulphadiazine are rationalized on the basis of crystal packing analysis, potential energy calculations and estimates of the activation energy for desolvation. Hydrogen bonding patterns between host molecules in the clathrates are compared with those occurring in two polymorphic forms of the parent sulphonamide.

INTRODUCTION

Solvent inclusion during crystallization of drug molecules is common and may result in species which on desolvation either retain their crystal form or transform to another crystal form. This has practical implications in the pharmaceutical industry.¹

Several studies relating to the solid state properties of the solvated forms of 5-methoxysulphadiazine (**1**), *N*'-(5-methoxy-2-pyrimidinyl)sulphanilamide (SMD), have appeared in the literature.^{2–5} A study of the

dioxane solvate (**1a**) and the chloroform solvate (**1b**) by thermal analysis² revealed that these species are unusually stable, losing solvent at approximately 100°C. Optical examination³ and X-ray photographic studies⁴ led to the assignment of these solvates to the monoclinic and orthorhombic systems respectively. Partially conflicting results were reported for the stoichiometric composition of **1b**,^{2,4} but both **1a** and **1b** were reported to yield polymorphic Form I of SMD on desolvation. More recently, the preparation of the tetrahydrofuran (THF) solvate (**1c**) and the cyclohexanone solvate of SMD, their unusual thermal stability, as well as their desolvation to Form I or Form II, or a mixture of these polymorphs, were reported.⁵ Reviewing the literature describing these solvates, we were led to consider several unresolved questions, including that of their exact stoichiometric compositions, the nature of solvent inclusion, reasons for their unusual thermal stability and the predominance of Form I as the desolvation product. In order to address these questions, we have accordingly prepared single crystals of three representative solvates, **1a–1c**, and have determined their structures by X-ray diffraction. The structural results together with thermo-analytical data, crystal packing considerations and kinetic data for desolvation are presented to explain the nature of solvent inclusion and structural changes accompanying decomposition of the solvates. The relationship between the hydrogen bonding arrangements involving the host SMD molecules in the solvated species and those occurring in Form I⁶ and Form II of SMD is described.



RESULTS AND DISCUSSION

Both thermogravimetric and single crystal X-ray analyses indicated 1:1 host:guest stoichiometry for **1a–1c**. Figures 1, 2 and 3 are perspective views of the asymmetric units, with the common nomenclature for the host SMD shown in Figure 1. Corresponding

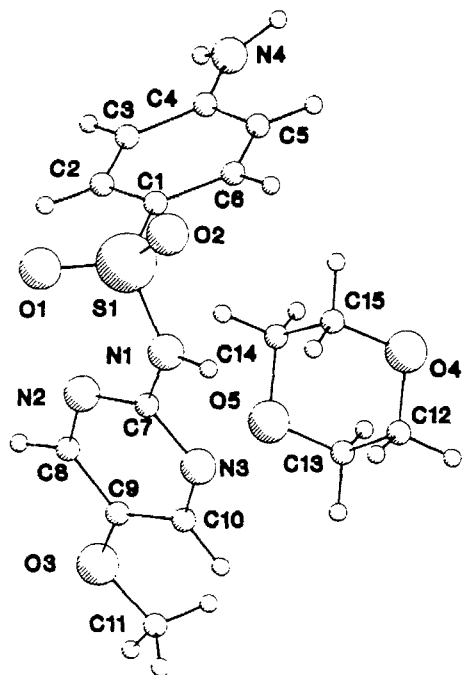


Figure 1 Structure of the asymmetric unit in **1a**.

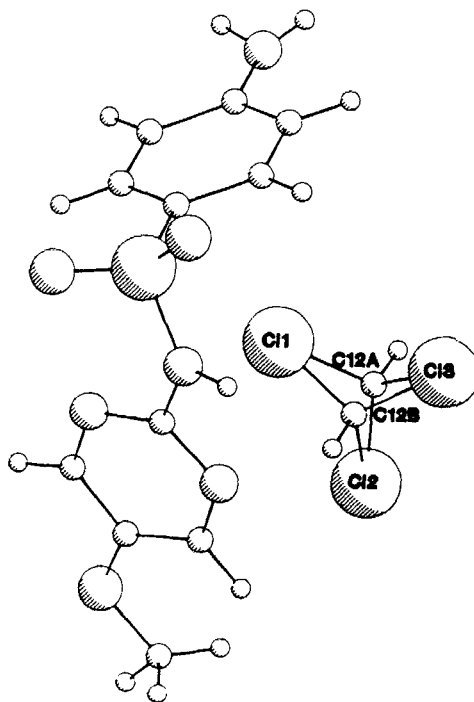


Figure 2 Structure of the asymmetric unit in **1b**.

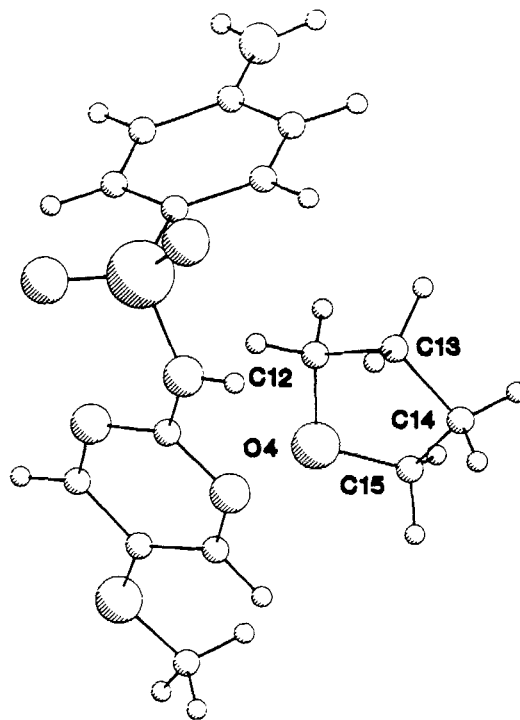


Figure 3 Structure of the asymmetric unit in **1c**.

Table 1 Torsion angles (degrees) defining the conformation of SMD

	<i>1a</i>	<i>1b</i>	<i>1c</i>
C(2)–C(1)–S(1)–N(1)	104.6 (3)	104.6 (6)	107.7 (3)
C(1)–S(1)–N(1)–C(7)	–64.8 (3)	–64.6 (6)	–59.2 (3)
S(1)–N(1)–C(7)–N(2)	–14.4 (5)	–20.0 (9)	–25.8 (4)
C(8)–C(9)–O(3)–C(11)	172.6 (3)	177.5 (7)	175.4 (3)

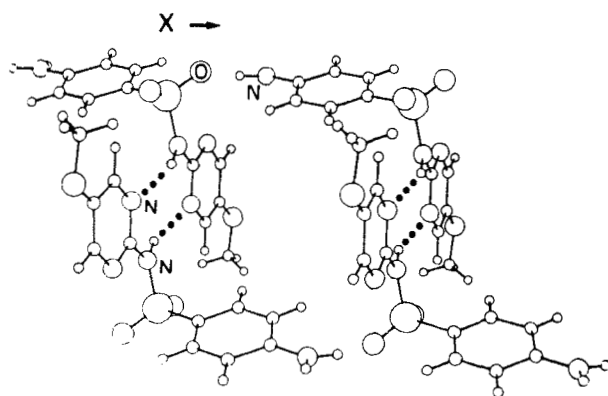
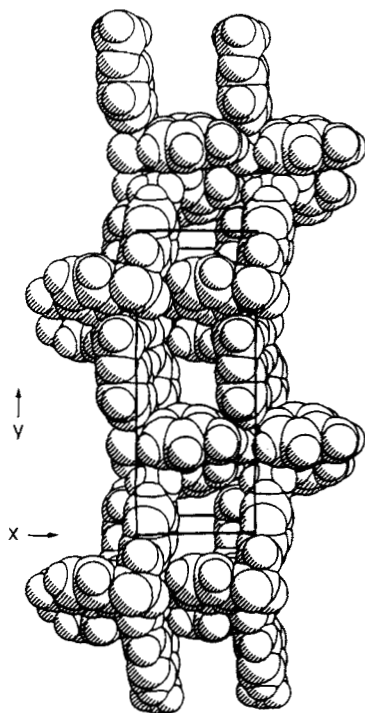
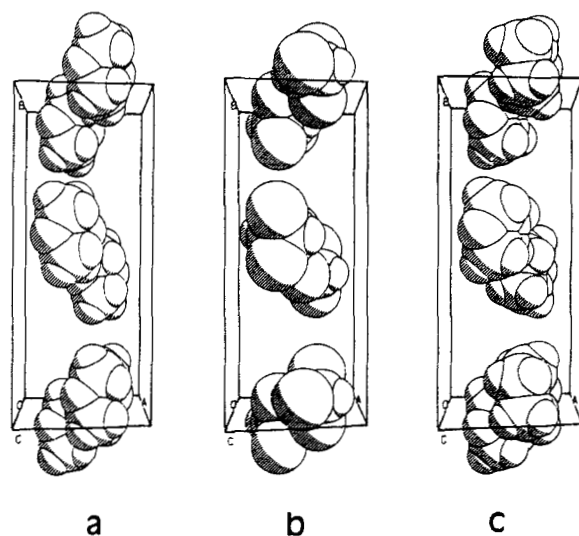
interatomic distances and bond angles in the SMD molecule are in close agreement in **1a–1c** and lie in the expected ranges.⁶ The molecular conformation of SMD is defined by the torsion angles listed in Table 1. In **1a** and **1c**, the guest dioxane and THF molecules adopt chair and envelope conformations respectively. Torsion angles in the dioxane molecule are in the range 57–66°, while for THF the torsion angle about the bond C(13)–C(14) is –8.0(6)° and the C–C–O–C torsion angles are 26.2(6)° and –30.9(6)°. In **1b**, the C atom of the guest CHCl₃ molecule is disordered, occupying two alternative sites symmetrically disposed on either side of the plane of the Cl atoms.

Analysis of the crystal packing in **1a–1c** shows that the host SMD forms centrosymmetric dimers via a pair of N–H⋯N hydrogen bonds. Dimers related by translation along *a* give rise to a cage-like structure in which the guest molecules are accommodated. This is shown in Figure 4 for **1a**. Hydrogen bond details are listed in Table 2. Figure 5, showing the resultant

Table 2 Hydrogen bond data: distances in Å, angles (final column) in degrees, with e.s.d.s in parentheses

	Donor-H	Donor...acceptor	H...acceptor	Donor-H...acceptor
1a				
N(1)-H(1)···N(3 ⁱ)	1.00 (4)	2.898 (5)	1.983 (5)	150.9 (3)
1b				
N(1)-H(1)···N(3 ⁱ)	1.00 (8)	2.914 (8)	2.050 (9)	143.1 (6)
C(12A)-H(12A)···O(3 ⁱⁱ)	0.99 (1)	3.34 (2)	2.356 (6)	170.9 (7)
C(12B)-H(12B)···N(3 ⁱⁱⁱ)	0.98 (2)	3.37 (2)	2.473 (5)	151.0 (6)
1c				
N(1)-H(1)···N(3 ⁱ)	0.84 (3)	2.936 (4)	2.10 (3)	174 (3)
N(4)-H(42)···N(2 ^{iv})	0.90 (4)	3.170 (5)	2.48 (4)	134 (3)

(i) $-x, 1-y, 1-z$.
 (ii) $-x, 1-y, 1-z$.
 (iii) $1-x, 1-y, 1-z$.
 (iv) $1+x, y, z$.


Figure 4 Cavity formation by translation of centrosymmetric SMD dimers. Broken lines represent hydrogen bonds.

Figure 5 Space-filling representation of the common host framework showing cavities.

Figure 6 Cavity occupation by guest molecules: (a) dioxane, (b) CHCl_3 , (c) THF.

host framework common to all three solvates, clearly reveals host cavities, while Figure 6 shows cavity occupation by the respective pairs of centrosymmetrically related guest molecules. In **1a** and **1c** there are no hydrogen bonds linking the guest molecules to the hydrogen-bonded host framework. In one of the disordered orientations of the CHCl_3 molecule in **1b**, there is evidence of host-guest $\text{O}\cdots\text{H}-\text{C}$ hydrogen bonding, while in the other a possible $\text{N}\cdots\text{H}-\text{C}$ hydrogen bond is indicated (Table 2). These interactions are weak but may play a role in preventing large-amplitude motions of the included CHCl_3 molecules. The solvates may thus be described as co-ordination-assisted clathrates, with **1b** showing a slight tendency towards co-ordination-clathration.⁷

Differential scanning calorimetry (DSC) reveals two endotherms upon heating any of the solvates. A representative example is shown in Figure 7, in which

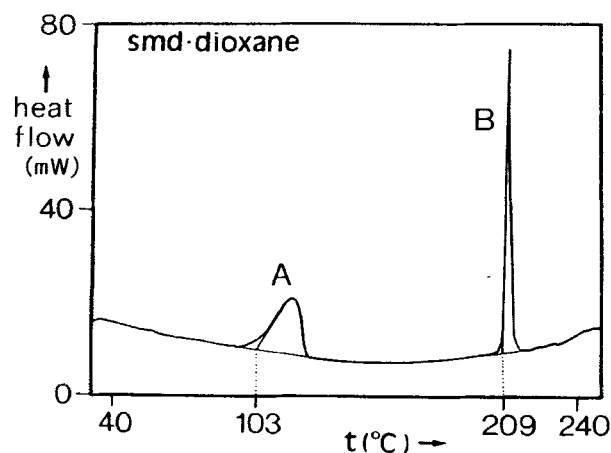


Figure 7 DSC trace for **1a**: peak A, desolvation; peak B, fusion of SMD.

Table 3 Thermodynamic data for desolvation of **1a–1c**

Compound	$t_{\text{onset, A}}$ (°C)	ΔH_A (kJ mol ⁻¹)	$t_{\text{onset, B}}$ (°C)	ΔH_B (kJ mol ⁻¹)
1a	103	40	209	29
1b	96	32	211	27
1c	88	41	210	29

peak A corresponds to the desolvation step and peak B to the fusion of SMD. Onset temperatures and enthalpy changes for these transitions are listed in Table 3. Desolvation onset temperatures for **1a–1c** lie in a higher and narrower range than the boiling points of their corresponding pure guest liquids (dioxane 101°C; CHCl₃, 63°C; THF, 67°C), confirming the thermal stabilities of the solvates. Constant values obtained for the parameters describing the fusion of SMD indicate that desolvation of **1a–1c** yields the same species. X-ray powder diffraction analysis of **1a** and **1b** after desolvation yielded the powder pattern of polymorphic Form I of SMD, in accordance with previous findings.^{2,4} By the same method, we observed that **1c** also yields Form I exclusively on desolvation.

The close similarity in structure and behaviour of these solvates on heating prompted further investigation of the mechanism for desolvation. The cavity topology was studied using the program OPEC.⁸ Van der Waals radii were assigned to the host SMD atoms in the unit cell of the crystal of **1a** (taken as a representative structure) and the area occupied by the host alone on equally spaced sections was computed. Sectioning parallel to the unit cell *xz* and *yz* planes revealed no channels and hence no possibility of guest escape along the *x*- or *y*-directions in the crystal. The results of sectioning parallel to the *xy* plane are illustrated in Figure 8. There are two cavities per unit cell,

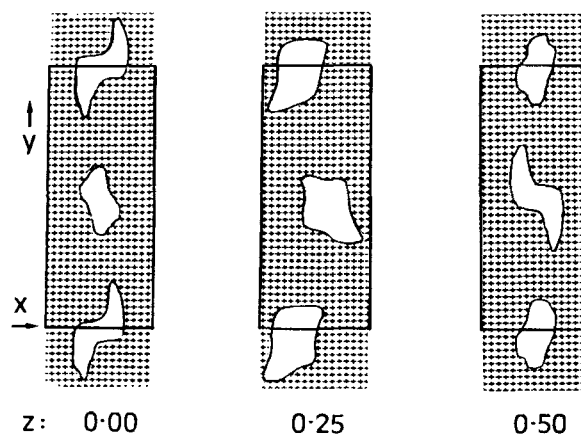


Figure 8 Cavity topology on *xy* sections of the unit cell of compound **1a** for the unique range $z = 0.0$ to 0.5 . The area occupied by the host molecules is boxed.

each accommodating two guest molecules. Narrow constrictions, of approximately 2 Å width only, occur at $z = 0.0$ for one cavity and at $z = 0.5$ for the symmetry-related cavity. The entrapment of relatively bulky solvent molecules in such cavities provides an explanation for the high threshold temperatures for desolvation of **1a–1c**. Migration of guest molecules through the crystal is impeded and desolvation must involve breakdown of the SMD host framework. The first conclusion was confirmed by potential energy calculations using program EENY,* which showed that when the guest dioxane molecules in **1a** are permitted to migrate along the *z* direction, allowing for their stepwise reorientation by energy minimization, they encounter insurmountable energy barriers on approaching the constrictions. Attempts were made to measure the activation energies for desolvation using a published procedure.⁹ This involves thermogravimetry (TG) at various heating rates (β) and plotting $\log \beta$ versus T^{-1} at several values of C , the fractional extent of decomposition. From the slopes of linear, parallel plots thus obtained, the activation energy E_a for the decomposition process may be calculated. Since the shapes of the TG curves are quite sensitive to sample preparation, this method was applied with only partial success. The most consistent results, shown in Figure 9, were obtained for **1c** and yielded an E_a value of 103(2) kJ mol⁻¹. Plots of $\log \beta$ versus T^{-1} for **1a** and **1b** showed some curvature, yielding less precise estimates for E_a of 102(9) and 94(19) kJ mol⁻¹ respectively. The estimated E_a values for **1a–1c** are nevertheless quite similar and support the hypothesis of a common mechanism for desolvation.

*EENY Potential Energy Program by W. D. S. Motherwell, University of Cambridge, U.K., 1974, unpublished.

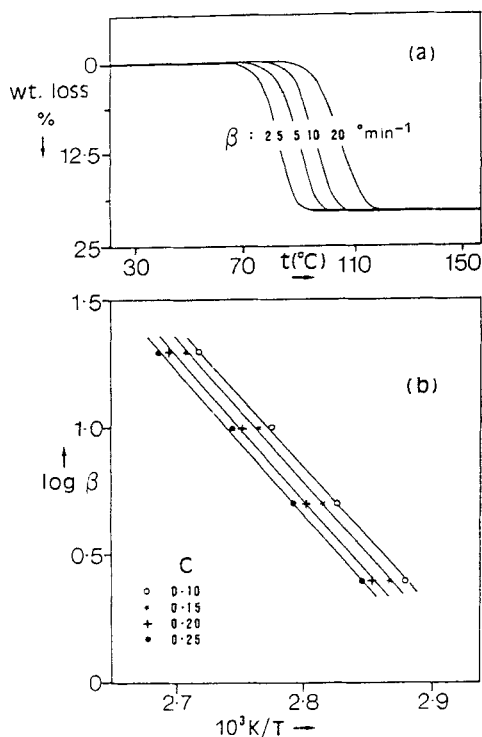


Figure 9 (a) TG traces for desolvation of **1c** at different heating rates (β); (b) Corresponding $\log \beta$ vs. T^{-1} plot at four values of C , the fractional extent of reaction.

Disruption of the host framework on desolvation of **1a–1c** is unequivocally confirmed when the crystal structures of the solvates are compared with that published for Form I.⁶ Whereas the repeating unit of SMD in the solvates is a centrosymmetric N–H \cdots N hydrogen-bonded motif (Fig 4), the motif in Form I, the desolvation product, is a dimer of SMD formed by one N–H \cdots O (sulphonyl) and one N–H \cdots N (pyrimidinyl) hydrogen bond (Fig 10).

During the course of this study, we isolated polymorphic Form II of SMD and determined its structure.¹⁰ We found that it is based on the same centrosymmetric dimer as that occurring in the solvates. Crystal stabilization of this dimer can therefore also be realized in the absence of solvent molecules.

EXPERIMENTAL SECTION

Synthesis and characterization of the compounds

SMD was purchased from Aldrich-Chemie, Steinheim. X-ray powder diffraction analysis showed it to be Form I.⁴ All solvents used were previously dried over molecular sieve. Each solvate was prepared by heating a solution of SMD in the appropriate solvent to boiling, followed by slow cooling in order to obtain large crystals. Masses of SMD and solvent volumes

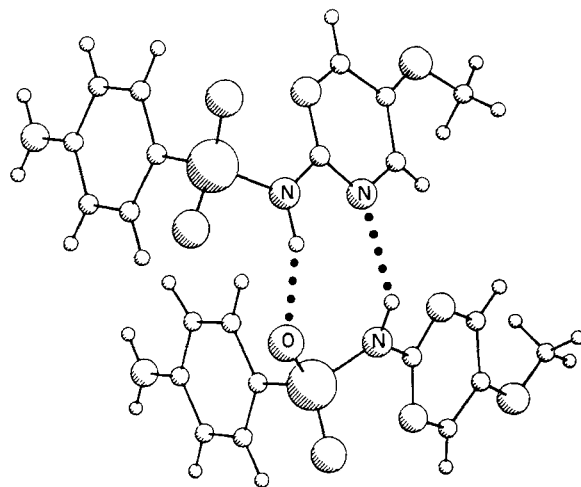


Figure 10 Structure of the SMD dimer in Form I. (Prepared from data in ref 6).

were as follows: **1a** 0.20 g, 10 cm³ dioxane; **1b** 0.05 g, 45 cm³ CHCl₃; **1c** 0.05 g, 16 cm³ THF. The identity of solvates **1a** and **1b** was initially established by comparing their X-ray powder patterns with those reported.⁴ Patterns were recorded on a Philips PW1050/80 goniometer with Ni-filtered Cu K α radiation ($\lambda = 1.5418 \text{ \AA}$) using a step scan of $0.1^\circ 2\theta$ over the 2θ range $6\text{--}40^\circ$ with 1° receiving and 1° divergence slits. Samples were ground and placed in Al holders. Thermomicroscopy on a Linkam TH600 hot stage coupled to a Linkam CO600 temperature controller revealed a change from colourless to opaque for all samples at approximately 100°C followed by melting at approximately 210°C . This behaviour is in accordance with that reported for the solvates.⁴ For TG and DSC analyses a Perkin Elmer PC7-Series Thermal Analysis System calibrated with indium and zinc was used. Sample masses for TGA ranged from 2 to 8 mg and for DSC 5 to 20 mg. Heating rates were in the range $5\text{--}20^\circ\text{C min}^{-1}$. Samples were placed in vented pans and the sample chamber was purged with high purity N₂ gas at a rate of $30 \text{ cm}^3 \text{ min}^{-1}$. The stoichiometry of the solvates was determined from TGA traces which indicated a single step desolvation in each case with the following percentage mass losses: **1a** 23.8, **1b** 29.6, **1c** 20.4. These values are in excellent agreement with the respective theoretical values of 23.9, 29.9 and 20.5 for 1:1 host:guest stoichiometry. Conclusive characterization was by single crystal X-ray diffraction which confirmed the identity of the included solvents as well as the stoichiometric compositions of **1a–1c**.

Crystallographic analyses and data collection. Precession X-ray photography showed that **1a–1c** were nearly isomorphous, crystallizing in space group $P2_1/c$,

Table 4 Data collection and refinement details

	<i>1a</i>	<i>1b</i>	<i>1c</i>
Formula	C ₁₁ H ₁₂ N ₄ O ₃ S·C ₄ H ₈ O ₂	C ₁₁ H ₁₂ N ₄ O ₃ S·CHCl ₃	C ₁₁ H ₁₂ N ₄ O ₃ S·C ₄ H ₈ O
<i>M_r</i>	368.41	399.67	352.41
Space Group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> , Å	8.056 (1)	8.129 (2)	8.020 (2)
<i>b</i> , Å	19.500 (1)	19.077 (2)	19.187 (2)
<i>c</i> , Å	11.252 (3)	11.256 (2)	11.175 (2)
β , deg	98.72 (2)	101.56 (1)	98.89 (2)
<i>V</i> , Å ³	1747.2 (5)	1710.1 (6)	1699.0 (6)
<i>Z</i>	4	4	4
<i>D</i> _{calc} , g/cm ³	1.401	1.552	1.378
μ (Mo K α), cm ⁻¹	2.09	6.71	2.07
<i>F</i> (000)	776	816	744
Crystal size, mm	0.31 × 0.44 × 0.47	0.16 × 0.22 × 0.34	0.34 × 0.28 × 0.22
Index range	±9; 0–23; 0–13	±9; 0–22; 0–13	±9; 0–22; 0–13
θ limits, deg	1–25	1–25	1–25
Standard intensity stability, %	–2.4	–6.8	–1.2
Vertical aperture, mm	4	4	4
Reflections measured	3346	3274	3272
Unique reflections	2761	2532	2610
<i>R</i> _{int}	0.015	0.062	0.024
<i>Observed data</i>			
<i>I</i> > 2 σ (<i>I</i>)	2290	1891	2030
Parameters refined	233	220	234
<i>R</i>	0.055	0.086	0.046
<i>R_w</i>	0.055	0.096	0.044
<i>S</i> (goodness of fit)	3.95	5.62	1.98
<i>g</i>	0.00	8.08 × 10 ⁻⁴	0.00
Mean shift/e.s.d.	0.005	0.010	0.001
$\Delta\rho$: min, max/eÅ ⁻³	–0.43, 0.38	–1.03, 0.92	–0.33, 0.24

No. 14 (from systematic absences $h0l, = 2n + 1$ and $0k0, k = 2n + 1$) with nearly identical cell dimensions. For intensity data collection a single crystal of each solvate was mounted on an Enraf–Nonius CAD4 diffractometer operating in the $\omega - 2\theta$ scan mode and using graphite monochromated Mo K α radiation ($\lambda = 0.7107$ Å).

Accurate unit cell parameters were obtained by least-squares analysis of the settings of 24 reflections with θ in the range 16–17°. Data were collected with variable scan width ($\omega = 0.85 + 0.35 \tan \theta$ deg), aperture width ($1.12 + 1.05 \tan \theta$ mm) and speed with a minimum of 40 s per reflection. In each case three reference reflections were monitored periodically for intensity and orientation control. All data were corrected for Lorentz polarization effects. Absorption corrections ranging from 0.9832 to 0.9991 were applied to the data for **1b** using the program EAC of the Enraf–Nonius Structure Determination Package.¹¹ Data collection details and structure refinement parameters are listed in Table 4.

Structure determination and refinements. The structure of **1b** was determined by direct methods using the

SHELXS86 program.¹² All non-hydrogen atoms of the SMD molecule were revealed in an E-map based on 797 reflections with $E > 1.2$. Difference Fourier maps were used to locate the solvent molecule which was disordered, atom C(12) occupying two alternative positions on either side of the plane of ordered Cl atoms. Most of the hydrogen atoms were located in difference Fourier syntheses but were generally added in idealized positions with C–H and N–H 1.00 Å and assigned common variable U_{iso} values for chemically similar groups. The final model included the following features: all non-hydrogen atoms anisotropic except C(12A) and C(12B), the latter refining isotropically to $U_{\text{iso}} = 0.12$ Å² after their site-occupancy factors had settled to 0.655 and 0.345 respectively; bond length constraints of 2.73 Å ($\sigma = 0.01$ Å) for Cl⋯Cl and 1.65 Å ($\sigma = 0.01$ Å) for C–Cl. For **1a** and **1c**, the initial models comprised the refined atomic positions of the SMD molecule obtained for **1b**. Rapid convergence followed and the solvent molecules were located in difference Fourier maps. Six discrete peaks for the atoms of the dioxane molecule were found for **1a**. Fairly high thermal motion was observed for these atoms on refinement but there was no evidence of an

alternative orientation of the solvent molecule. Final refinement included anisotropic thermal parameters for all non-hydrogen atoms and distance constraints of 1.42 Å ($\sigma = 0.01$ Å) and 1.48 Å ($\sigma = 0.01$ Å) respectively for the C–O and C–C bonds in dioxane. Refinement of **1c** presented no difficulties. Positional and thermal parameters for the THF molecules were well-behaved and difference maps revealed all the attached hydrogen atoms. Treatment of the hydrogen atoms in **1a** and **1c** was similar to that of **1b** above. All least-squares refinements were carried out using the SHELX76 program,¹³ in which $\Sigma w \| F_o \| - |k F_c|^2$ was minimized. Weighting schemes of the form $w = (\sigma^2 F_o + g F_o^2)^{-1}$ were employed to yield a constant distribution of $\Sigma w (\Delta F)^2$ with $\sin \theta$ and $(F_o/F_{\max})^{1/2}$. Complex neutral atomic scattering factors were used.¹⁴ Other programs used were PARST¹⁵ and PLUTO.*

ACKNOWLEDGEMENT

Financial assistance from the Foundation for Research Development (Pretoria) and the University of Cape Town is gratefully acknowledged. We thank the Computing Centre, University of Cape Town, for the use of the VAX computer.

* PLUTO program for plotting molecular and crystal structures by W. D. S. Motherwell and W. Clegg, University of Cambridge, U.K., 1978, unpublished.

SUPPLEMENTARY MATERIAL AVAILABLE

Tables of final atomic co-ordinates, thermal parameters, bond lengths, bond angles and torsion angles (18 pages) and structure factor tables (38 pages) for **1a**, **1b** and **1c** are available from M.R.C.

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