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THERMAL STUDIES OF SOLVENT EXCHANGE IN ISOSTRUCTURAL SOLVATES OF A TETROXOPRIM-SULFAMETROLE COMPLEX

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Abstract

Isostructural solvates of the 1:1 molecular complex between the antibacterial drugs tetroxoprim (TXP) and sulfametrole (SMTR) with formulae TXP·SMTR·CH_3OH (I), TXP·SMTR·C_2H_5OH (II) and TXP·SMTR·H_2O (III), were investigated to establish their propensity for guest exchange. Separate exposure of powdered (I), (II) and (III) to a saturated atmosphere of each solvent of the complementary solvate pair at ambient temperature resulted in reversible solvent exchange in all cases. DSC and TG were the methods of choice for monitoring the exchange processes since (I)–(III) have distinct onset temperatures of desolvation and characteristic mass losses. Interpretation of the results in terms of the known locations of the solvent molecules in crystals of (I)–(III) led to the conclusion that solvent exchange probably proceeds by a co-operative mechanism involving material transport through channels while the common host framework is maintained.

Keywords: DSC, HSM, isostructurality, solvates, solvent exchange, TG

Introduction

For two or more substances of different chemical composition, the term 'isostructurality' means very similar crystallographic properties i.e. substantially the same crystal structure. Crystal isostructurality is synonymous with isomorphism and is the opposite of polymorphism, which instead refers to the ability of an element or chemical compound to occur in different crystal structures. Since 1993, isostructurality has proven to be much more frequent than previously expected, in particular among pharmaceuticals ([1] and refs therein).

Isostructurality can exist between two drugs such as, for example, erythromycin A dihydrate and erythromycin B dihydrate, which differ at a molecular level by a single hydroxyl group only but show very similar crystallographic data and powder X-ray

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diffraction (PXRD) patterns [2]. An analogous isostructural relationship was found for ethyl paraben and propyl paraben, that was associated with their ability to form substitutional solid solutions [3]. Isostructurality was also found for inclusion complexes of organic molecules in cyclodextrins (CDs) and exploited for possible identification of new complexes through assignment to a given isostructurality series [4]. The ethylene glycol·8.0H_2O and glycerol·7.2H_2O inclusion complexes with β-CD are isostructural, with a cage-type crystal packing isomorphous with that of β-CD hydrate [5].

A relationship of isostructurality can occur between a crystalline desolvation product of a solvate (desolvated solvate) and the parent solvate. Of particular interest are the desolvates of pharmaceutical hydrates [6], that can be defined as organic crystalline substances containing stoichiometric amounts of water of crystallization when in equilibrium with the saturated solution, but which upon exposure to ambient air or when dried, lose most of the solvent without converting to a different crystalline form and thus maintain essentially the same three-dimensional arrangement as the original crystal. A case in point is the aforementioned antibiotic erythromycin A dihydrate, which is not only isostructural with the homologue erythromycin B dihydrate, but also with its own dehydration product [2].

Notwithstanding the crystallographic and structural analogies between the desolvation product of a hydrate and the parent hydrate, their physical properties may differ, even considerably. The void spaces created within the desolvated crystal consequent to solvent loss reduce the packing efficiency and the lattice energy, rendering this form less stable than the solvated structure. The molecular vacuum created by desolvation can be counterbalanced through a density-increasing process either by incorporation of small molecules in the structure (resolvation) or by structural relaxation (annealing). This explains why the formation of an isostructural desolvate can lead to an extremely hygroscopic solid or one of reduced chemical stability. Bauer *et al*. [7] demonstrated dissolution failures for erythromycin dihydrate tablet formulations as a consequence of gradual interaction between the active and the excipient $Mg(OH)_2$. The importance of desolvated solvates as a variant of pharmaceutical solids along with polymorphs, hydrates and amorphous forms, also from the regulatory point of view, has been stressed by Byrn *et al*. [8]. Among inorganic compounds, a notable case of a desolvated solvate is gypsum, a hydrated calcium sulphate with composition $CaSO_4·2H_2O$ whose dehydrated forms range isostructurally from $CaSO_4·2H_2O$ to $CaSO_4$, the hemihydrate $CaSO_4·0.5H_2O$ being the stable form known commercially as plaster of Paris and in nature as bassainite [9]. Among the additives of pharmaceutical formulations, β-CD, which is reported in the National Formulary 22 [10], shows a water content per β-CD molecule ranging from 12.3H_2O at 100% to about 9.4H_2O at 15% humidity with no substantial modification of the crystalline structure, which at very low humidities collapses irreversibly due to loss of water [11].

Solvated crystalline forms of a drug with two or more different solvents represent a further class of potentially isostructural compounds. Actually, associated crystals tend to be isostructural since different guest molecules may often be incorporated into a host lattice without substantially changing its structure [1]. Antibiotics belonging to the macrolide class tend to form a series of solvates of this type, for example

dirithromycin which forms six isostructural solvates (e.g. with ethanol, 1-propanol, 2-propanol, 1-butanol, acetone and 2-butanone), with nearly identical PXRD patterns [12]. Other isostructural stoichiometric solvates include those of succinylsulfathiazole with 1-butanol and 1-pentanol [13], whereas isostructural non-stoichiometric solvates are e.g. those of alprazolam with ethanol and acetonitrile [14], of tetroxoprim with water, ethanol and methanol [15], and those of erythromycin with acetone and methylethylketone [16].

This report focuses on solvates of the molecular complex TXP·SMTR formed between the antibacterials tetroxoprim (TXP, 2,4-diamino-5-[3,5-dimethoxy-4-(2-methoxyethoxy)benzyl]pyrimidine) and sulfametrole (SMTR, 4-amino-N-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide). Recently we characterized two isostructural stoichiometric solvates of TXP·SMTR with methanol and ethanol, as well as two polymorphic modifications of the analogous monohydrate, described as 'nearly isostructural' with the former pair [17]. The methanolate showed a tendency to exchange the solvation solvent with water upon exposure to ambient air and gradually transformed into the hydrate crystalline phase, stable at room temperature. In this paper, we report on a quantitative investigation of solvent exchange between isostructural (methanolate to ethanolate and vice versa) and 'nearly isostructural' (methanolate or ethanolate to hydrate and vice versa) forms of the molecular complex TXP·SMTR by exposure to a saturated atmosphere of the entering solvent at room temperature. Thermal analysis (differential scanning calorimetry, DSC; thermogravimetric analysis, TG) proved to be a valuable technique to distinguish isostructural (and obviously 'nearly isostructural') solvates, and therefore to follow the course of solvent exchange between solvates. Furthermore, the known location of the solvent molecules in the crystal structures of all the solvates enabled us to reconcile the common structural features with thermal behaviour and thermodynamic data from DSC and TG experiments. Finally, our hypothesis on the mechanism of desolvation by heating was confirmed by thermomicroscopic analysis (HSM). Previous studies employing the DSC technique to monitor guest exchange in isostructural solvates [18, 19] involved larger guest molecules and synthetic diol host compounds.

Experimental

DSC was performed using a Mettler Star^e system equipped with a DSC821^e Module on 3–5 mg (Mettler M3 microbalance) samples in aluminium pans with pierced lids under static air. Analog empty pans were used as reference. The heating rate was 10 K min^{-1} over the temperature range 30–200°C. Measurements were performed in triplicate (relative *SD*±5%).

Thermogravimetric analysis (TG) was carried out with a Mettler TA 4000 apparatus equipped with a TG 50 cell at a heating rate of 10 K min^{-1} on 7–10 mg samples in open alumina crucibles in the temperature range 30–200°C. Measurements were performed in triplicate (relative *SD*±2.5%).

Powder X-ray diffraction (PXRD) patterns were recorded on a Philips PW 1800/10 diffractometer equipped with a Microvax 2000 and APD 1700 software in the range

$2°<2\theta<50°$ with a scan speed of 0.02° 2θ s^{-1}. CuK_{α}-radiation [$\lambda(CuK_{\alpha,1})$=1.54060 Å, $(CuK_{\alpha,2})$=1.54439 Å] was employed (Monochromator: graphite crystal).

Solvent exchange was studied by exposure to saturated atmospheres of water, ethanol and methanol of ≈1 g of each solvate sample (granulometric fraction <180 μm) spread on Petri dishes in a desiccator at room temperature (22°C).

Mid-IR (400–4000 cm^{-1}) spectra were recorded by the Nujol mull method using a FTIR Perkin Elmer model 1605 spectrophotometer (resolution 4 cm^{-1}).

Isostructurality indices Π, $I_i(n)$ and I_v were calculated [1]. The index $I_i(n)$ was computed for n=42 (TXP·SMTR including major disorder components), n=43 [TXP·SMTR·O(solvent)], and n=44 [TXP·SMTR·O–C(alcohol)]. All three solvates crystallize in the space group P(-1) with Z=2 [17]. All coordinates were transformed to 1–x, 1–y, 1–z to select the molecules closest to the crystallographic origin. For calculation of I_v and $I_i(n\ x\ Z)$, molecules at x, y, z and 1–x, 1–y, 1–z were used.

Results and discussion

Structural data

The crystallographic asymmetric unit in the solvates TXP·SMTR with methanol (I) and ethanol (II) and in the hydrate stable at room temperature, TXP·SMTR·H_2O (III), consists of one formula unit of the complex TXP·SMTR and one molecule of the corresponding solvent [17] (Fig. 1). Solvates (I) and (II) have identical space groups,

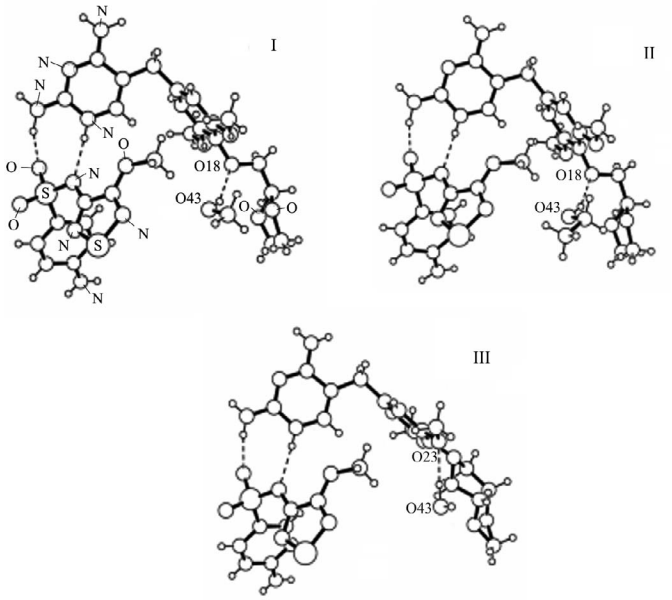


Fig. 1 Crystallographic asymmetric units in the title solvates: TXP·SMTR·CH_3OH (I), TXP·SMTR·C_2H_5OH (II) and TXP·SMTR·H_2O (III). The key for heteroatom labelling is shown in (I)

Table 1 Isostructurality indices calculated for the tetroxoprim–sulfametrole molecular complex methanolate TXP·SMTR·CH_3OH (I), ethanolate TXP·SMTR·C_2H_5OH (II), and hydrate TXP·SMTR·H_2O (III)

Structures	Π	$I_1(42)$	$I_1(43)$	$I_1(44)$	$I_1(42\times2)$	$I_1(43\times2)$	$I_1(44\times2)$	I_v	I_v^{max}
(I)–(II)	0.007	78.3	77.9	77.3	68.5	68.6	68.4	89	98
(II)–(III)	0.010	–6.0	–7.1		–47.4	–47.5		66	96
(I)–(III)	0.004	12.8	11.2		–20.8	–21.3		71	98

very similar unit cell dimensions and almost identical locations of molecules in their respective crystals [17]. A high degree of isostructurality between (I) and (II) was indicated by the unit-cell similarity index (Π) and the isostructurality indices $I(n)$ and I_v according to Fábián and Kálmán [1] (Table 1), a result which was expected from detailed comparison of the crystal structures and reflected in the analogies of the PXRD patterns (Fig. 2) and IR spectra (Fig. 3).

Replacement of MeOH and EtOH molecules by water molecules within the framework of the host TXP·SMTR to form the hydrate TXP·SMTR·H_2O results in a slight structural deformation, sufficient to produce PXRD patterns and IR spectra that permit the new phase to be distinguished from the pair of isostructural

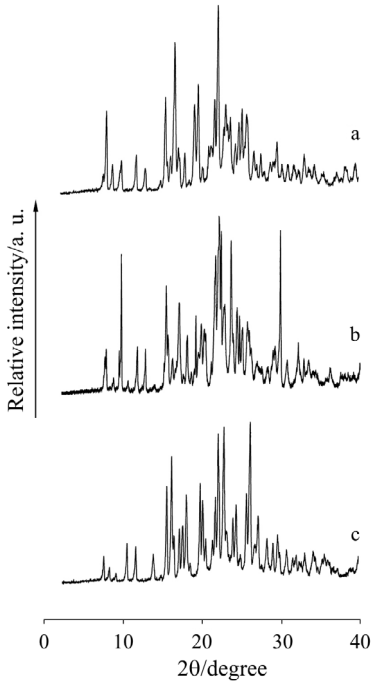


Fig. 2 PXRD patterns for a – TXP·SMTR·CH_3OH (I), b – TXP·SMTR·C_2H_5OH (II) and c – TXP·SMTR·H_2O (III)

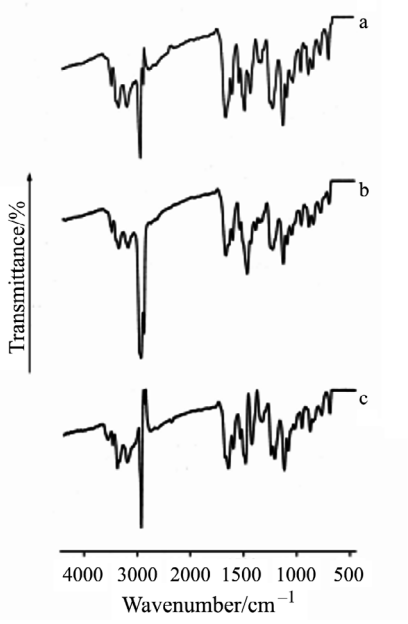


Fig. 3 FT-IR spectra for a – TXP·SMTR·CH_3OH (I), b – TXP·SMTR·C_2H_5OH (II) and c – TXP·SMTR·H_2O (III)

alcoholates. The overall structure of the hydrate is, nevertheless, closely related to that of the methanolate and ethanolate [17], even though the level of isostructurality between (I) and (III), and between (II) and (III) is significantly less than that between (I) and (II) (Table 1, parameter I_v). As evident from Fig. 1 and Table 1, the isostructurality of (I) and (II) extends even to the positions of atoms common to the included solvent molecules and to their mode of binding, though the lengths of the hydrogen bonds in which they participate differ significantly [17]. In particular, the hydrogen bond between the hydroxyl group of the solvent and the ethoxy-oxygen atom O18 of TXP in the methanolate (O43···O18, 2.872(4) Å) is significantly shorter than the corresponding hydrogen bond in the ethanolate (O43···O18, 2.941(2) Å) (Fig. 1). Consequently, the MeOH molecule in (I) is more tightly bound than the EtOH molecule in (II). On the other hand, in the hydrated complex (III) the greater hydrogen bonding capacity of the water molecule involves replacement of the common hydrogen bond occurring in (I) and (II) by the hydrogen bond O(water)···O23(methoxy, 2.882(4) Å), and formation of two other hydrogen bonds with symmetry-related host molecules. In addition, a new intermolecular hydrogen bond N–H···N, having no counterpart in the alcoholates, is created in the hydrate [17]. The framework of molecules of TXP·SMTR held together by hydrogen bonds in (III) is nevertheless very similar to that observed in the alcoholate structures and the water molecules occupy isolated sites analogous to those occupied by MeOH and EtOH molecules in their respective solvates.

Thermal data

The stronger interaction between the hydroxyl group of the solvent and atom O18 of TXP in the methanolate (I) compared with the situation in the ethanolate (II), as quantified above, is reflected in the higher onset temperature of desolvation of TXP·SMTR·CH_3OH (126.3(4)°C), compared with that for TXP·SMTR·C_2H_5OH (115(3)°C) (Fig. 4). Thus, upon heating, following loosening and rupturing of the hy-

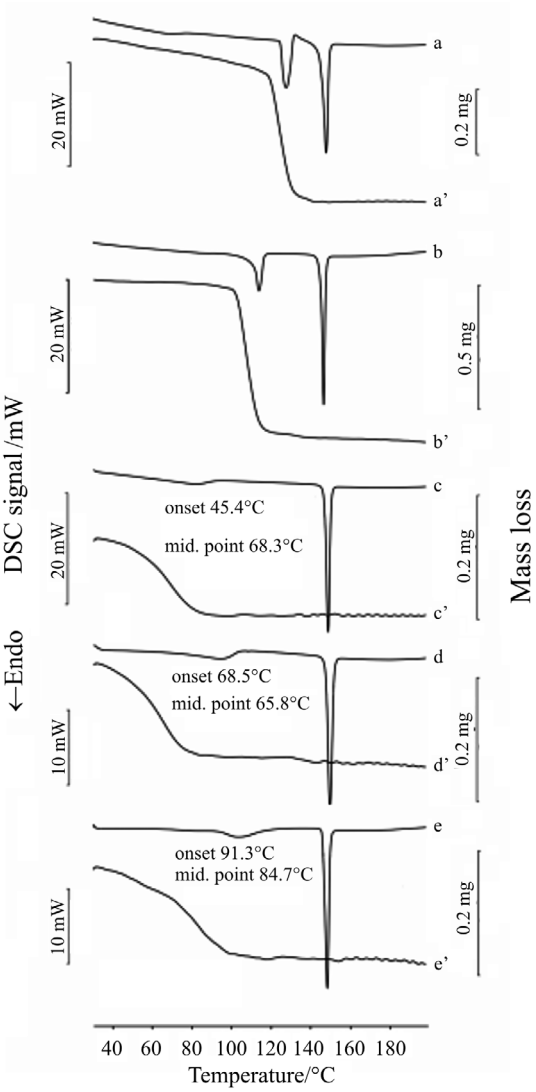


Fig. 4 DSC and corresponding TG curves for: a, a' – TXP·SMTR·CH_3OH (I), b, b' – TXP·SMTR·C_2H_5OH (II), c, c' – TXP·SMTR·H_2O (III) and variability in dehydration behaviour of d, d' and e, e' – TXP·SMTR·H_2O (III)

drogen bonds between host and guest, the diffusion of the ethanol molecules, with their greater steric bulk, through the common host framework accounts for the higher value of the enthalpy of vaporisation of the bound solvent required for complete desolvation of TXP·SMTR·C_2H_5OH ($\Delta H_{S,EtOH}$=59(5) kJ mol^{-1} *vs*. $\Delta H_{S,MeOH}$= 48(2) kJ mol^{-1}) [17]. The structural similarity between the hydrate (III) and the solvates (I) and (II), including the positions of the water molecules in isolated sites analogous to those of the molecules MeOH and EtOH in their respective solvates, translates into TXP·SMTR···water interactions that are ~20% stronger than those between water molecules in the liquid state [17]. However, the DSC behaviour of the hydrated complex is surprising, in that, in contrast to what is observed for the two alcoholate complexes, the dehydration is characterised not only by a relatively low and variable onset temperature, but also proceeds over a rather wide temperature range (Fig. 4). The TG mass losses for the three TXP·SMTR·H_2O samples of 2.72, 2.96 and 2.75% (Fig. 4, curves c', d', e') were, however, similar and close to the calculated value for the monohydrate complex (2.82%). The TG mass losses of 5.12% for TXP·SMTR·CH_3OH and 7.08% for TXP·SMTR·C_2H_5OH (Fig. 4, curves a', b') were also in agreement with the calculated values for a 1:1 TXP·SMTR:solvent stoichiometry (4.91 and 6.91%, respectively).

Movement of solvent molecules in the crystalline solvates

Generally, the solvent molecules in a crystalline solvate move through permanent channels or tunnels whose sizes influence the rate of solvent escape. In the methanolate (I) and ethanolate (II) complexes the location of the solvent molecules in isolated sites, as shown by the narrow profile of the desolvation endotherms and confirmed by X-ray analysis [17], seems at first sight to exclude any possible movement of MeOH or EtOH through the crystal without destroying the crystal structure. However, a careful examination of the sections drawn with van der Waals radii through the respective unit cells, specifically those at intervals of 1.6 Å shown in Fig. 5 [17] reveals the existence of narrow channels (unshaded areas) in the regions occupied by the MeOH and EtOH molecules through which these solvent molecules can migrate, particularly upon heating, when small conformational changes in the host framework can widen the channels to such an extent as to permit diffusion of the solvent molecules through the crystal.

In corresponding sections through the unit cell at 1.6 Å intervals (which practically span the range of the water molecule) of the hydrate (III) one notes the existence of analogous channels in the region occupied by the water molecule (Fig. 5). The relative ease of dehydration can reasonably be explained on the basis of the smaller size of the H_2O molecule, which permits it to migrate through such channels more easily than the more bulky MeOH and EtOH molecules. β-cyclodextrin hydrate is another solid in which water molecules can migrate despite the absence of permanent diffusion channels [11].

The experimentally observed variable onset temperature for dehydration of (III) (Fig. 4) is presumed to be due to differences in the concentrations of crystal defects

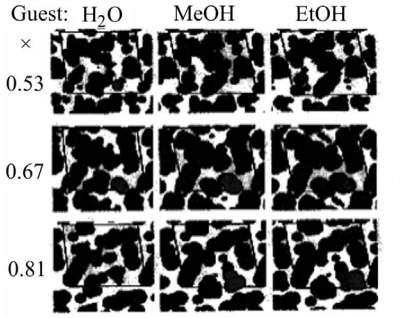


Fig. 5 Three sections projected down the *a*-axis (fractional co-ordinate *x*) and drawn at 1.6 Å intervals through the respective unit cells in TXP·SMTR·H_2O (III) (left), TXP·SMTR·CH_3OH (I) (middle) and TXP·SMTR·C_2H_5OH (II) (right) [17]. Lighter shaded regions represent the common TXP·SMTR framework and black regions the corresponding solvent molecules. All atoms are drawn with appropriate areas determined by their apparent van der Waals radii at each section

occurring in various preparations of the hydrate. The apparent anomaly of tight binding between water molecules and the bimolecular complex TXP·SMTR and the mobility of the water molecules within the crystal is thus resolved, further allowing for the possibility of mutual solvent exchange between the hydrate complex and the alcoholate complexes. Movement of solvent within crystals of the alcoholates (I and II) and the hydrate (III) upon heating, as well as the complete transformation into the anhydrous complex, were evident from thermomicroscopy (Fig. 6).

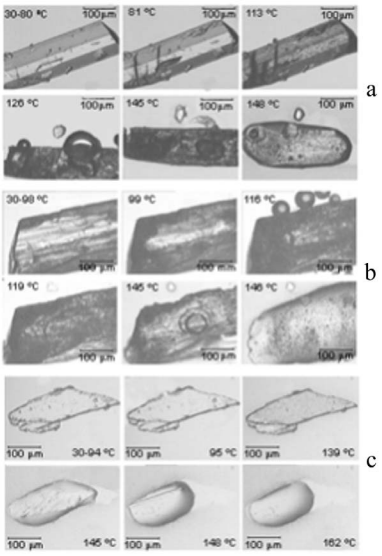


Fig. 6 HSM photomicrographs of the solvates a – TXP·SMTR·CH_3OH (I), b – TXP·SMTR·C_2H_5OH (II) and c – TXP·SMTR·H_2O (III) recorded at various temperatures

Retention of the initial crystal shape (and hence the main structural features) until just before fusion and escape of the molecules of methanol and ethanol from the crystal centre to the periphery are in accord with a co-operative thermal desolvation mechanism. The latter is best described as quasi-topotactic, rather than destructive or reconstructive (i.e. nucleation and growth mechanism) [20, 21]. HSM observation of the evolution of microcrystals of TXP·SMTR solvates upon heating under ambient atmosphere from room temperature to 200°C shows that the overall shape of the initial particle is preserved. The formation of cracks is likely due to macroscopic strains produced by escape of solvent molecules.

Solvent exchange in the crystalline solvates

On exposing the methanolate complex (Fig. 7, curve a': mass loss 5.12%) to an atmosphere saturated with ethanol at ambient temperature, it was possible to demonstrate experimentally the gradual exchange of solvent in the solid phase right up to the point of complete transformation to the ethanolate (Fig. 7, curve c': mass loss 6.85%). Thus, the elevated partial pressure of ethanol (entering solvent) in the

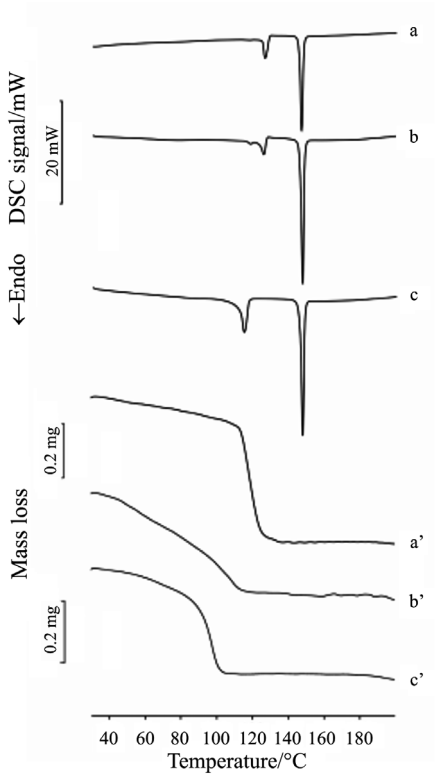


Fig. 7 DSC and corresponding TG curves of TXP·SMTR·CH_3OH (I) exposed to saturated atmosphere of ethanol after times t=0 (a, a'), t=8 h (b, b'), t=24 h (c, c')

atmosphere surrounding the methanolate is the driving force for release of methanol molecules, which are then replaced by ethanol molecules with retention of the crystal structure. The analogous process of exchange was observed starting with the ethanolate and exposing it to an atmosphere saturated with methanol at ambient temperature (data not shown).

On the other hand, when the methanolate complex (Fig. 8, curve a': mass loss 5.42%) is exposed to an atmosphere saturated with water, it gradually transforms into the hydrate (Fig. 8, curve d': mass loss 2.39%). The analogous process of exchange is observed starting with the ethanolate and exposing it to a saturated atmosphere of water at ambient temperature (data not shown). The high vapour pressure of water was probably responsible for the gradual replacement of the molecules of methanol and ethanol by water molecules within the crystal until the exact 1:1 host:guest stoichiometry was reached. In a saturated atmosphere of water, the vapour

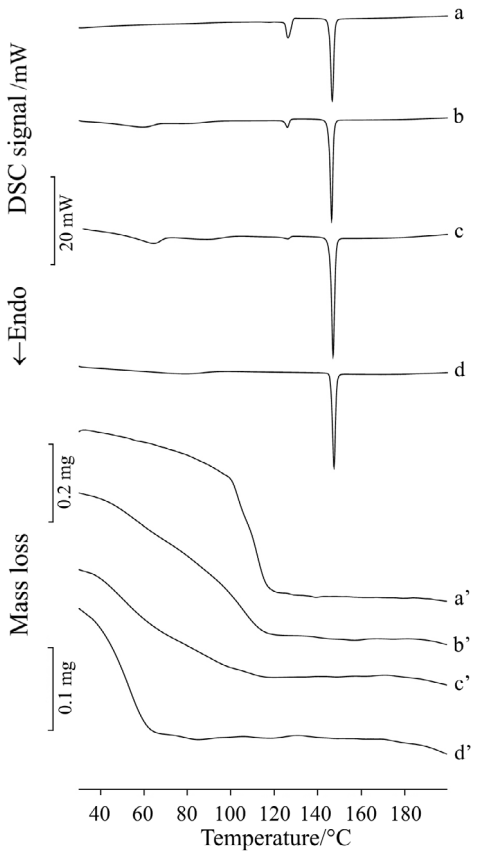


Fig. 8 DSC and corresponding TG curves of TXP·SMTR·CH_3OH (I) exposed to saturated atmosphere of water after times t=0 (a, a'), t=3 h (b, b'), t=19 h (c, c'), t=24 h (d, d')

pressure of the solvent (MeOH or EtOH) in the alcoholate crystals becomes so high as to overcome the energy of the respective hydrogen bonds, and water molecules concurrently replace the H-bonds involving ethanol/methanol by water···complex H-bonds. Thus, similarly to the mechanism described for roxithromycin acetonitrile solvate and hydrate [20], the exchange of ethanol/methanol with water 'proceeds in a cooperative, non destructive way', most solvent molecules being either evacuated or inserted along parallel structural channels in the crystal. The methanol complex also gradually transforms into the hydrate upon exposure to ambient air (45–50% RH), while the ethanolate complex is stable under these conditions, probably due to the larger steric bulk of the molecules to be replaced. By exposing the hydrate complex (Fig. 9, curve a': mass loss 3.06%) to an atmosphere saturated with methanol at ambient temperature it has been possible to show experimentally gradual solvent ex-

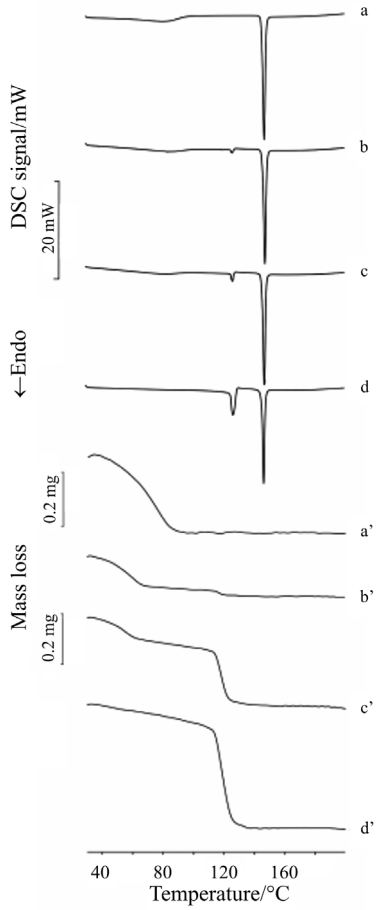
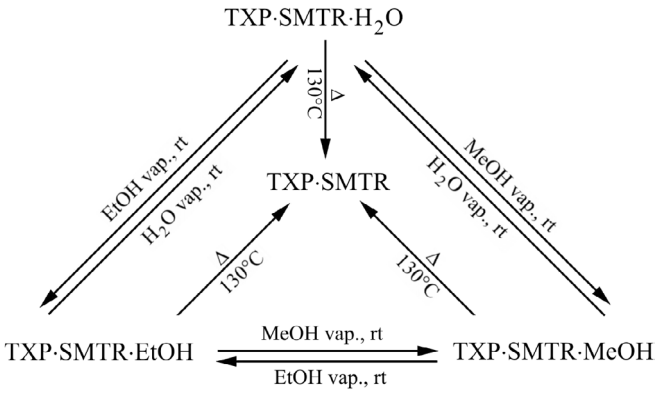


Fig. 9 DSC and corresponding TG curves of TXP·SMTR·H_2O (III) exposed to saturated atmosphere of methanol after times t=0 (a, a'), t=2 h (b, b'), t=18 h (c, c'), t=24 h (d, d')

change, leading to complete transformation to the methanolate (Fig. 9, curve d': mass loss 5.12%). The analogous process of exchange was observed when the hydrate complex was exposed to an atmosphere saturated with ethanol (data not shown).



Scheme 1

The solid–solid transformations among isostructural (or 'nearly isostructural') solvates in the form of microcrystalline powders, when exposed to an atmosphere saturated with the replacing solvent, proceed with a smooth and reversible exchange of the solvent (Scheme 1) which probably involves transport of material within channels without substantially altering the crystalline structure, and thus via a topotactic or co-operative mechanism [20]. By heating in a hot air oven at 130°C for 2 h, TXP·SMTR·CH_3OH, TXP·SMTR·C_2H_5OH and TXP·SMTR·H_2O transform into a common anhydrous crystalline form TXP·SMTR (Scheme 1).

Conclusions

The qualitative terms 'isostructural' and 'nearly isostructural' previously used to describe the crystallographic relationships among the title solvates [17] have been replaced by isostructurality indices whose computed values confirm that the two alcoholates share a significantly higher degree of isostructurality than they do individually with the hydrate phase. The possibility of characterizing isostructural solvates which are indistinguishable from their PXRD patterns and FT-IR spectra using thermoanalytical methods (DSC and TG) has allowed the process of solvent exchange to be followed, subjecting samples of microcrystalline powders of a solvated complex at ambient temperature to an atmosphere saturated with a replacing solvent. Solvent exchange is a reversible process associated with very limited structural changes, as confirmed by the evolution of complex solvate microcrystals upon heating under ambient atmosphere. A thermally very stable solvate such as the methanolate of TXP·SMTR can transform into the hydrate in the solid phase upon exposure to ambient air at ambient temperature i.e. without direct contact with the liquid phase. This may be

of interest from the viewpoint of drug formulation since in general, apart from the technological aspects, a hydrate presents less favourable bioavailability characteristics (dissolution rate in water) than a solvate containing a solvent that is miscible with water.

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