

CHIRAL RESOLUTION BY CRYSTALLIZATION OF HOST–GUEST SUPRAMOLECULAR COMPLEXES A paradoxal situation with an efficient discrimination despite structural similarities

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Abstract

The crystallization behaviour and the physical characterization of supramolecular complexes formed between permethylated- α -cyclodextrin (TM α -CD) and the enantiomers of phenylethanol (PE) are investigated. According to crystal structure analyses, complexes containing the pure guest enantiomers are almost isomorphous, indicating that the host presents a poor ability to distinguish PE enantiomers at a molecular level. Nevertheless, crystallizations from racemic PE in water induce an efficient chiral discrimination and allow the enantio-separation of the guests despite the existence of a solid solution revealed by XRPD and coupled TG-DSC analyses. The enantiodifferentiation is explained by solubility differences between the two diastereomeric complexes in the studied temperature range. Moreover, it is shown that the diastereomeric complex TM α -CD/(S)-PE crystallizes in two distinct phases: a monohydrate and an anhydrous form, with a transition temperature close to 37°C. The insertion of a water molecule in the crystals grown below 37°C does not involve any other change of the crystal packing nor of the molecular conformation, but leads to different crystal growth mechanisms inducing different morphologies and distinct thermal behaviours.

Keywords: chiral recognition mechanism, crystal structure, enantioseparation, host-guest inclusion, permethylated cyclodextrin, solid solution, solubility

Introduction

Among the various methods designed to separate at a preparative scale the two enantiomers of a racemic mixture, the formation of host–guest supramolecular complexes prepared with cyclodextrins (CDs) as chiral hosts has long ago been recognized as an interesting possibility [1]. The chiral resolution mechanism is based on the formation

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of two diastereomeric compounds [2] exhibiting different physical properties, including solubilities. Nevertheless, it appeared from various studies [3–5] that the applicability of this procedure with native (i.e., not chemically modified) cyclodextrins was rather poor, since it usually led to limited enantioenrichments rather than to complete chiral resolutions.

During the two last decades, crystal structure investigations have provided insights at a molecular level on the stereodifferentiation and the associated chiral recognition phenomena [6, 7]. Some of these structural studies, performed with native or permethylated CDs (2,3,6-tri-O-methylated CDs, TM-CDs hereafter), have revealed important conformational differences of the macrocycles between these two families, which were mainly attributed to sterical hindrances and to the absence of strong intramolecular hydrogen bonds for TM-CDs [8]. Owing to the resulting higher molecular flexibility of these compounds, it was also postulated [7] that they should present, compared to native CDs, an improved ability for chiral discrimination, because of an easier conformational adjustment to each guest enantiomer (so-called 'induced-fit'). This statement has been confirmed recently [9, 10] with the first published example where each of the two enantiomers of a spiro compound could be isolated from a racemic mixture by simple crystallizations of host-guest complexes with TM α -CD and TM β -CD, respectively.

Harata and coworkers have deduced from their structural investigations that the ability of TM-CDs to achieve chiral resolutions was also dependant on the developed formula and the molecular size of the guest, because of the necessity for the host to recognize three points of each enantiomer [11, 12]. By comparing the crystal structures of complexes formed between TM α -CD and each enantiomer of two related compounds (mandelic acid and phenylethanol, MA and PE hereafter), they have shown that the presence of a carboxy group in MA was responsible for a reduced penetration of the (*S*) enantiomer, resulting in distinct crystal structures. In the case of PE, it was argued that TM α -CD could not recognize the chirality of this guest, therefore leading to isomorphous structures for the two diastereomeric complexes. However, despite similar crystal growth conditions, morphologies, crystallographic parameters and packings, one of these complexes (TM α -CD/(*R*)-PE) was shown to crystallize as an anhydrous form, whereas the other corresponds to a monohydrate (TM α -CD/(*S*)-PE/H₂O). A careful analysis of host-guest relative orientations in these structures also revealed that the two aromatic moieties of the guest enantiomers are 12° apart in the host, but this limited structural difference is not assumed to induce significant changes between the behaviours of the two diastereomeric compounds.

In order to confirm the interpretations of the author in terms of required conditions for chiral recognition and resolution, we have undertaken a complementary study of the complexes formed in the quaternary system (TM α -CD/(*R*)-PE/(*S*)-PE/water). Owing to the existence of different hydration stoichiometries (monohydrate and anhydrous forms), we were interested in investigating the influence of this parameter on the solubility, and the consequences for possible enantioseparation. Indeed, our recent studies [13, 14] have shown that a suitable characterization of true diastereomeric complexes formed with TM β -CD could account for the possibility to resolve a racemic mixture by means of

successive recrystallizations. It was postulated from this previous work that the chiral resolution mechanism can be divided into a couple of different types of molecular interactions: (i) in solution, a molecular recognition phenomenon is required, leading to the existence of host-guest complexes with specific interactions and geometries, and (ii) the solvated diastereomeric complexes may then lead to a supramolecular recognition phenomenon based on the construction of a 3D periodic lattice. An amplification of small energetic differences among the solvated species can thus result from the packing of these crystallizing units. Moreover, the crystallization can proceed via the incorporation of other building blocks such as solvent(s), non-encapsulated guests [15], which enlarges the possibilities to enhance the stereoselectivity of the solid-state packing.

In the present case, our initial hypothesis was that the existence of a solid solution should limit significantly the possibility to resolve a racemic mixture of PE by means of simple crystallizations.

Experimental section

Materials

Permethylation of native α -cyclodextrin was carried out by adapting to this smaller macrocycle the procedure published by Schurig *et al.* for β -cyclodextrin [16]. Crude samples were recrystallized two times in cold water. Permethylation of the α -cyclodextrin was controlled by NMR spectroscopy (permethylation fraction >97%). Pure enantiomers and racemic phenylethanol ('ChiProsTM', 99%) were purchased from Lancaster.

Crystallization procedures

Preparation of solid-state supramolecular entities

Supramolecular complexes were obtained from aqueous solutions containing a (1:1) molar ratio of host and guest components. After the dissolution of TM α -CD in water at room temperature, the addition of PE induced the appearance of an emulsion which disappeared after about one hour under magnetic stirring, revealing the formation of solvated supramolecular complexes. Crystallizations were induced by heating these solutions, in consistency with the retrograde solubility of complexes formed with usual (α , β and γ) permethylated cyclodextrins. The temperature was controlled by using a programmable cryo-thermostat with an accuracy of $\pm 0.5^\circ\text{C}$. The suspensions were maintained under stirring until filtration, which were performed at the crystallization temperature in order to avoid partial dissolution.

Influence of temperature and crystallization durations on the enantioenrichment effect

In order to investigate the influence of these parameters in identical and well-identified conditions, crystallizations were performed from three mother solutions with identical dimensionless supersaturation ($\beta=1.5$) and volume (10 mL of water). The quantities of

host and guest components required to obtain identical supersaturations at three different temperatures were deduced from solubility measurements performed close to the racemic composition by using the gravimetric method (Table 1).

Table 1 Solubility values of complexes formed between (*rac*)-PE and TM α -CD close to the racemic composition (e.e. <7%) as a function of temperature

Temperature/°C	30	35	42	45
Solubility values/mass% (accuracy $\pm 0.15\%$)	2.7	2.1	1.4	1.2

The total volume of each solution was separated in four aliquots of 2 mL, and each portion was heated at the desired temperature under magnetic stirring. Isothermal filtrations were performed after different crystallization durations (5, 15, 45, 90 min), and solid-state samples were analyzed by various techniques (see below).

Characterization of solid-state samples and analytical methods

Enantiomeric excesses were determined by chiral gas chromatography analyses. Preliminary dissociation of the complexes was required in order to avoid the injection in the column of the dextrin derivatives which can undergo pyrolysis in analytical conditions. For this purpose, a micro-flash-chromatography on silica gel was carried out (eluant=ethyl acetate/cyclohexane (15:85); $Rf_{(PE)}=0.3$; $Rf_{(TM\alpha-CD)}=0.1$). Chiral analyses were performed on a Packard 5890 instrument equipped with a Supelco Betadex 120[®] column (383 K, isothermal run, injector and detector temperature 523 K, Helium carrier gas, $\mu_{opt.}=30 \text{ cm s}^{-1}$).

Host-guest stoichiometries were established by ¹H NMR spectroscopy performed in CDCl₃ on a Bruker AC 300[®] spectrometer.

Crystalline solid phases were analysed by means of X-ray powder diffraction recorded on a Siemens D5005[®] diffractometer equipped with a copper source at room temperature. The raw spectra were processed with the EVA software (vers. 8.0).

The thermal behaviour of solid powders was investigated by simultaneous TG-DSC experiments, using a Netzsch STA 409 PC[®] apparatus (aluminium crucible 30 μ L, sample mass $16 \pm 0.5 \text{ mg}$, with a heating rate of 5 K min^{-1} and a nitrogen flow of 50 mL min^{-1}). When necessary, single crystals were smoothly ground prior to TG-DSC analysis.

Hot stage microscopy (HSM) observations were performed with a Nikon optical microscope equipped with a digital camera, at a magnification range from 20 to 50, and at a heating rate of 5 K min^{-1} .

Structural investigations

Crystal structure determinations were carried out at room temperature by means of single crystal X-ray diffraction, using a Bruker Smart Apex[®] system equipped with a monochromated MoK α source (0.71073 Å) and a CCD detector. Space group determinations,

structure solutions and refinements were carried out with the SHELX-TL program package [17]. All non-hydrogen atoms were refined anisotropically and hydrogen atom positions were calculated without further refinement.

Structural descriptions were performed with the modelling software Cerius² (v. 4.6, Accelrys Inc., 2001) implemented on a O2 Silicon Graphics workstation.

Results and discussion

Enantioenrichment by crystallization of supramolecular complexes in the system (TM α -CD/(rac)-PE/water)

Although it was deduced from previous structural studies [12] that no chiral recognition could be expected in the present case, the ability of permethylated α -cyclodextrin (TM α -CD) to resolve partially a racemic mixture of PE by host-guest complexation was investigated by means of simple crystallization experiments. In order to induce the crystallization of supramolecular entities, these experiments were performed according to a procedure previously used with permethylated β -cyclodextrin [13]. ¹H NMR analyses confirmed that the obtained solid samples were made of supramolecular complexes with a (1:1) stoichiometry, and the comparison of their XRPD patterns with that simulated from published crystal structures with the Cerius² software indicated that identical crystal forms had been obtained.

Surprisingly, chiral GC analyses of the solids obtained from these preliminary experiments revealed that significant enantioenrichments had occurred, with enantiomeric excesses (e.e.) ranging from 20 to 35% in favour of the (*S*)-PE enantiomer. It was therefore decided to evaluate more accurately the impact of temperature and crystallization durations on this discrimination, at a constant supersaturation. For this purpose, solubility values in the temperature range 30–45°C were determined close to the racemic composition (Table 1), and allowed to perform further experiments in well-established conditions. The crystallization procedure was reproduced at 35, 40 and 45°C, so that the evolution of the enantiomeric composition in the collected samples *vs.* crystallization durations and temperature could be evaluated (Fig. 1).

This study does not validate the above-mentioned assumptions regarding the inability of TM α -CD to discriminate the PE enantiomers. Indeed, the behaviour observed here is similar to that described in a case where distinct diastereomeric compounds had been characterized [14], with an important chiral discrimination (e.e. \approx 40%) during the first minutes of crystallization, and a decrease to about 25% of the enantiomeric excess in the solid phase as soon as the crystallization lasts 45 min or more. Simultaneously, the crystallization yield increases, but it seems that, whatever the temperature, an equilibrium is reached after about 45 min of crystallization since the enantiomeric excess does not change any more. It also appears from Fig. 1 that enantioenrichment is not sensitive to the crystallization temperature in the range 35–45°C. Actually, the enantioenrichment probably results from significant aqueous solubility differences between the enantiomerically pure complexes TM α -CD/(*R*)-PE and TM α -CD/(*S*)-PE (possibly hydrated, [12]), although this interpretation is poorly consistent with the assumed high structural similarities, since the lat-

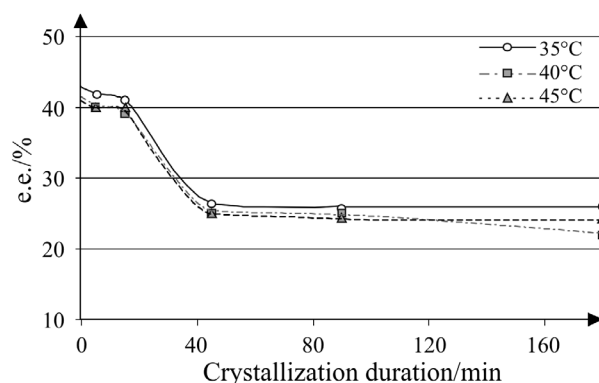


Fig. 1 Enantiomeric excess (e.e.) vs. crystallisation duration for the complexes formed between (*rac*)-PE and TM α -CD at different temperatures. The enantiomer in excess is the (*S*)-PE

ter should induce the existence of supramolecular crystalline materials exhibiting almost identical physico-chemical properties.

From these results, it could be envisaged to perform a complete resolution of a racemic PE through the formation of host-guest supramolecular complexes with TM α -CD, by means of successive recrystallizations. An almost complete resolution (e.e. $\geq 97\%$, Fig. 2) could be achieved after 7 crystallization runs of 45 min each, at 35°C and initial dimensionless supersaturation $\beta=2$, by using a procedure similar to that elaborated in the case of para-bromophenylethanol with TM β -CD [14]. It had been established in this previous study that chiral resolution was associated to different inclusion geometries and crystal packings, leading to different physical properties. This type of explanation should not hold in the present case.

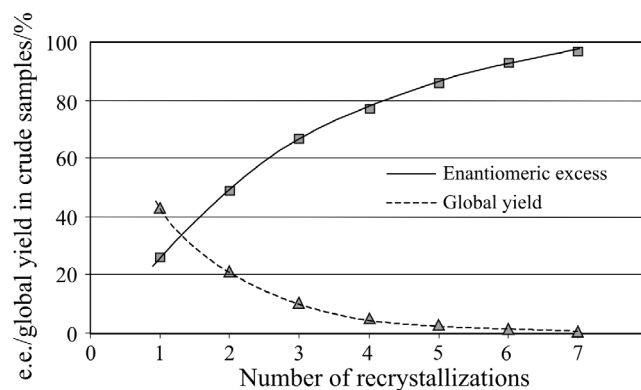


Fig. 2 Evolution of enantiomeric excess and global crystallization yield (dashed) for successive crystallizations of TM α -CD/PE complexes at 35°C. The enantiomer in excess is the (*S*)-PE

Thermal behaviour of solid-state samples as a function of enantiomeric composition

The comparison between experimental XRPD patterns of complexes containing various proportions of the two guest enantiomers showed, in consistency with structural data, that these solids could not be differentiated by this technique.

Since thermal methods were previously shown to provide reliable data for the study of host-guest complexation with cyclodextrins [18], simultaneous TG-DSC experiments were carried out on samples of known enantiomeric compositions (100% (*R*)-PE; 70/30-(*R*)/(*S*)-PE; 46/54-(*R*)/(*S*)-PE; 100% (*S*)-PE) with the aim to characterize these crystalline solids. The studied samples were prepared by crystallizations at 40°C, according to the procedure depicted above (Experimental section).

Whatever the enantiomeric composition of the samples, their thermal behaviour can be described as the superimposition of two endothermic phenomena in the range 120–180°C (Fig. 3). One of the thermal events is a broad phenomenon covering this temperature range, associated to a mass loss of approximately 8.9%, which indicates a continuous dissociation of the complexes resulting from the vaporization of PE (calculated mass% of PE: 9.06%). The departure of the guest component in this temperature range was confirmed by NMR spectroscopy analyses.

By contrast with this decomposition phenomenon which is not sensitive to the enantiomeric composition of the samples, the other endothermic phenomenon has a more definite shape and is clearly dependent on the proportion of the two enantiomers of PE, varying continuously but not linearly from 133°C for TM α -CD/(*R*)-PE to 151°C for TM α -CD/(*S*)-PE (onset temperatures). From HSM observations, it could be established that each of these thermal events is due to a fusion-recrystallization process. This continuous shift of onset temperatures suggests that a solid solution in the binary section (TM α -CD/(*R*)-PE–TM α -CD/(*S*)-PE) could exist below 100°C, i.e. prior to the thermal decomposition of the complexes, in agreement with the established structural similarities.

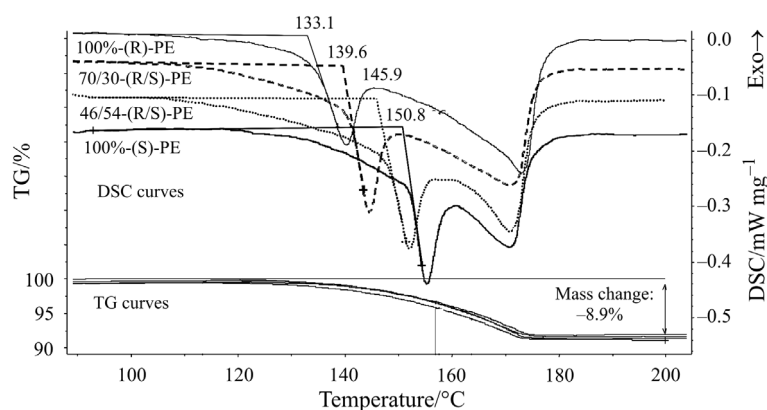


Fig. 3 Simultaneous TG/DSC analyses depicting the behaviours of solid-state TM α -CD/PE complexes as a function of their enantiomeric composition (heating rate 5 K min⁻¹)

These TG-DSC experiments have also revealed that no significant mass loss was observed below 100°C, so that the possible existence of a monohydrated form (described in [12]) could not be assessed. It should however be noticed that this mass loss would represent about 1.3%, which is close to the limit of detection of the apparatus. In the temperature range 180–250°C, only the expected melting peak of TM α -CD could be observed at 218 \pm 2°C (data not shown).

Solubility curves of enantiomerically pure complexes

In order to understand the unexpected chiral discrimination depicted above, the solubilities of pure complexes (TM α -CD/(*R*)-PE and TM α -CD/(*S*)-PE) have been measured in the temperature range 30–55°C. The obtained solubility curves are shown in Fig. 4 and reveal that the two curves do not exhibit similar evolutions as a function of temperature. Indeed, the solubility curve of TM α -CD/(*R*)-PE departs only slightly from linearity, whereas two distinct segments are observed for TM α -CD/(*S*)-PE, with a slope change at a temperature close to 37°C. This non continuous behaviour indicates that, for this compound, the saturated solution is probably in equilibrium with two distinct solid phases, below and above this temperature. Nevertheless, these phases could not be differentiated by XRPD nor by TG-DSC analyses.

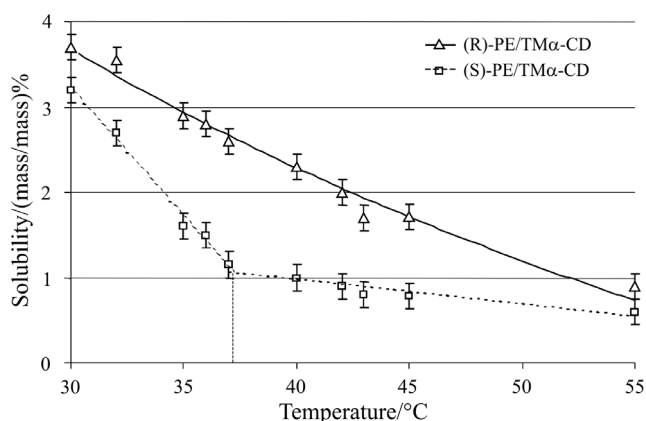


Fig. 4 Aqueous solubility curves of the enantiomerically pure TM α -CD/PE complexes, measured by the gravimetric method

The absence of linearity for TM α -CD/(*S*)-PE induces that the solubility gap between the two complexes varies significantly with temperature (factor 1.2 at 30°C/2.3 at 37°C/2.0 at 42°C/1.5 at 55°C). It can also be assumed from these data that there should exist two temperatures (approximately 25 and 60°C) for which identical solubility values should be observed. If the solid phases obtained during crystallization experiments correspond to those of solubility measurements, this should induce the absence of any chiral discrimination at these temperatures. As a

confirmation of this trend, a crystallization experiment from (*rac*)-PE at 60°C led to a powder containing a 10% enantiomeric excess only for crystallization durations longer than 30 min.

Crystal growth studies and thermal analysis of ground single crystals

The probable existence of distinct solid phases for TM α -CD/(*S*)-PE (deduced from solubility measurements) was further investigated by means of comparative crystal growth studies performed with complexes containing the two pure enantiomers of PE in the temperature range 32–45°C.

Representative single crystals obtained at 35 and 40°C are presented in Fig. 5, showing that crystals made of TM α -CD/(*R*)-PE exhibit a prismatic and triangular habit whatever the growth temperature. In the case of TM α -CD/(*S*)-PE, crystal growth experiments revealed the formation of two distinct morphologies, below and above 37°C. At temperatures higher than 37°C, crystal habits are similar to that observed for TM α -CD/(*R*)-PE ('high-temperature' phase), whereas the morphologies obtained below 37°C are clearly different, and can be described as elongated or rod-shaped particles ('low-temperature' phase).

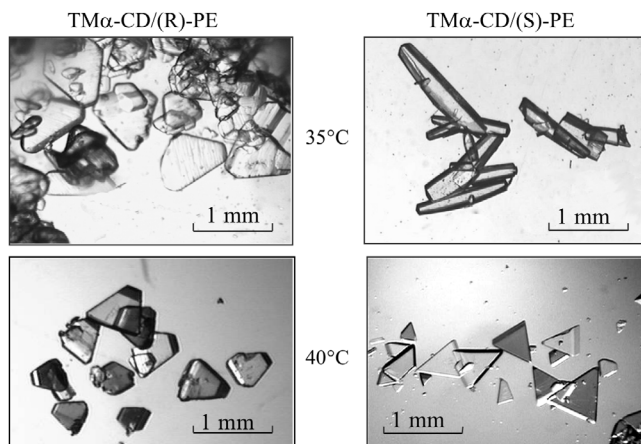


Fig. 5 Optical microscopy photographs depicting the crystal habits of enantiomerically pure complexes of TM α -CD/(*R*)-PE (left) and TM α -CD/(*S*)-PE (right) grown at different temperatures (upper: 35°C; lower: 40°C)

These data are consistent with our hypothesis, deduced from solubility measurements, regarding the existence of two different crystal phases for TM α -CD/(*S*)-PE. Nevertheless, XRPD analyses of smoothly ground crystals led to similar patterns for the three samples collected during crystal growth studies. It can be seen from the XRPD patterns presented in Fig. 6 that the peak intensities obtained with elongated crystals differ strongly from that collected with prismatic samples. This phenomenon can result from both instrumental and preferred orientation effects,

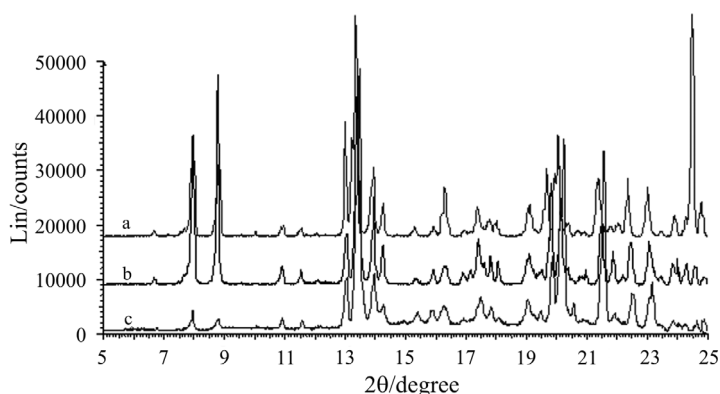


Fig. 6 Experimental XRPD patterns obtained from smoothly ground single crystals of a – TM α -CD/(R)-PE and b – TM α -CD/(S)-PE exhibiting either a prismatic or c – an elongated morphology

and does not allow to differentiate the phases since diffraction angles (2θ values) are clearly identical for these samples, which were therefore analysed by coupled TG-DSC techniques.

For both TM α -CD/(R)-PE and TM α -CD/(S)-PE complexes, the thermal behaviour of crystals exhibiting a prismatic habit is identical to that obtained from powders (Fig. 3), and can be distinguished by the shift of the melting/recrystallization peaks at 133 and 151°C, respectively. By contrast, crystals of TM α -CD/(S)-PE with an elongated morphology show a different thermal behaviour. Indeed, it appears from the TG curves presented in Fig. 7 that the vaporization of PE occurs with a rate of departure significantly slower than that of the other samples, and the associated broad phenomenon observed in DSC is of smaller magnitude. For similar amounts of material, PE is fully

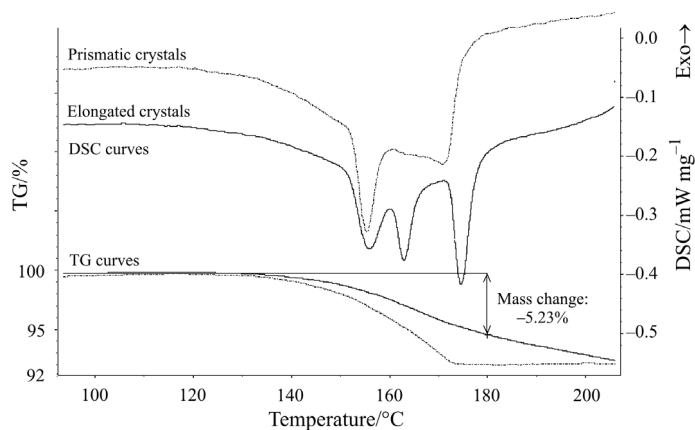


Fig. 7 Simultaneous TG/DSC analyses of smoothly ground single crystals for TM α -CD/(S)-PE complexes presenting either a prismatic (dashed lines) or an elongated morphology (continuous lines)

evaporated at 180°C (–8.9 mass/mass%) for samples with a prismatic morphology, whereas only about 5% are lost at this temperature in the case of elongated crystals, and a complete decomposition is reached at 218°C.

The comparison of the DSC curves for the two samples of TM α -CD/(S)-PE (Fig. 7) indicates that the first endothermic peak (onset 152°C) is common in the two cases. However, two supplementary thermal events are observed at 161 and 172°C (onset temperatures) for the complex exhibiting an elongated morphology. The interpretation of such behaviour is difficult to establish mainly because of the impossibility, due to the dissociation of the complexes, to perform XRPD analyses on the samples above 120°C. From hot stage microscopy experiments, it could be seen that the global shape of the particles is preserved between 160 and 200°C. Nevertheless, careful observations indicated that, above 160°C, each particle seems to be composed of two distinct regions, with an inner part presenting a physical aspect slightly different from that of a superficial layer. This observation could reveal the formation, after a partial departure of PE, of a solid layer coating the particle, which hinders further evaporation, and could therefore explain the slower dissociation rate for the elongated crystals of TM α -CD/(S)-PE. In the frame of this hypothesis, the two endothermic peaks at 161 and 172°C could result from fusions/recrystallizations of the complex remaining encapsulated in the inner part of the particles.

Crystal structure investigations and discussion

Despite highly similar XRPD patterns, the above results indicate that two distinct crystalline phases of the TM α -CD/(S)-PE complex can be obtained, and can be differentiated by their solubility curves, morphologies and thermal behaviours. Large and well-defined single crystals of these two phases were therefore selected for complete structural investigations by means of X-ray diffraction. The two crystal structures could be determined with a high accuracy, as established by the final *R* factors (Table 2). Complete structural data were deposited at the Cambridge Crystallographic Data Center and registered under the deposition numbers CCDC-230658 and CCDC-230659. Crystallographic parameters and main refinement data are collected in Table 2, from which it appears that unit cell dimensions are very close. Furthermore, the comparative analysis of molecular conformations, host-guest relative orientations and crystal packings revealed almost identical structural features. Nevertheless, it also appeared during the last refinement steps that a significant residual peak of electron density was present in the ‘low-temperature’ phase (elongated morphology), which could be attributed to the oxygen atom of a water molecule. This atom is actually found at the same location in the structure published by Harata [12] for the TM α -CD/(S)-PE/H₂O complex, so that the two structures can be considered as identical.

By contrast, no residual peak could be identified in the second crystal structure (‘high-temperature’ phase, prismatic habit), from which it can be established that the only significant difference between these structures consists of the presence or not of a water molecule. With reference to the monohydrate, the anhydrous phase can therefore be considered as an ‘isomorphous desolvate’ [19] at the transition temperature. In the

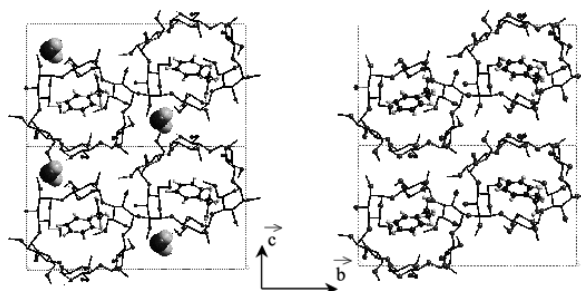
Table 2 Crystallographic data and measurement conditions for crystal structure analyses of TM α -CD/(S)-PE complexes with different morphologies, and comparison with published parameters [12] (all measurements carried out at room temperature)

Supramolecular complex	TM α -CD/(S)-PE	TM α -CD/(S)-PE, H ₂ O	TM α -CD/(S)-PE, H ₂ O [12]*
Formula	C ₅₄ H ₉₆ O ₃₀ ·C ₈ H ₁₀ O	C ₅₄ H ₉₆ O ₃₀ ·C ₈ H ₁₀ O·H ₂ O	C ₅₄ H ₉₆ O ₃₀ ·C ₈ H ₁₀ O·H ₂ O
Crystal habit	triangular/prismatic	rod-shaped/elongated	prismatic
Formula mass	1347.5 g mol ⁻¹	1365.5 g mol ⁻¹	1365.5 g mol ⁻¹
Unit cell dimensions (Monoclinic P2 ₁ , Z=2)	<i>a</i> =11.567 (6) Å <i>b</i> =23.725 (9) Å <i>c</i> =13.668 (6) Å β =106.37 (9)°	<i>a</i> =11.617 (5) Å <i>b</i> =23.721 (9) Å <i>c</i> =13.792 (7) Å β =106.42 (1)°	<i>a</i> =11.586 (3) Å <i>b</i> =23.641 (6) Å <i>c</i> =13.762 (3) Å β =106.45 (2)°
Volume	3599 Å ³	3646 Å ³	3615 Å ³
Nb of reflections collected/unique	22590/10308	29396/14249	4479 ($ F > 3\sigma F $)
Final <i>R</i> indices	<i>R</i> ₁ =0.0359 <i>wR</i> ₂ =0.0829	<i>R</i> ₁ =0.0454, <i>wR</i> ₂ =0.0945	<i>R</i> ₁ =0.073
Largest diffraction peak and hole	0.16/−0.11 e [−] Å ^{−3}	0.21/−0.26 e [−] Å ^{−3}	

*The crystal structures published in [12] can be retrieved from the Cambridge Structural Database (CSD) with refcodes JEJWOK (TM α -CD/(R)-PE) and JEJXAX (TM α -CD/(S)-PE, H₂O).

structure of the monohydrate, it can be seen from Fig. 8 that the water molecule is involved in two hydrogen bonds with neighbouring complexes (oxygen–oxygen distances: 2.96 and 3.07 Å), and therefore participates to the structural cohesion and lattice energy of the monohydrate phase via a periodic bond chain running along the *c*-axis.

The presence or not of this water molecule is the only explanation allowing to account for the solubility curves, and for the observed differences in terms of crystal habit and thermal behaviour between the diastereomeric phases. More precisely, it has to be envisaged that the insertion of water molecules in the crystal lattice during the growth of crystalline particles below 37°C could be responsible for a change in the crystal growth mechanism, resulting in the formation of elongated particles. It

**Fig. 8** Projection along the *a* axis of the almost isomorphous crystal structures of TM α -CD/(S)-PE complexes (left: monohydrate; right: anhydrous form)

should also be assumed that the thermal behaviour observed for this phase is a consequence of this morphological change, since a more difficult departure of PE molecules could be induced by a different crystal habit.

Hence, our interpretations deduced from crystal structure analyses reveal that the existence of two distinct phases, a monohydrate and an anhydrous form, for the $\text{TM}\alpha\text{-CD}/(S)\text{-PE}$ complex can explain the obtained solubility curves. In order to confirm that a true transition occurs between these phases close to 37°C , further crystal growth experiments were carried out. Single crystals presenting an elongated habit (grown at 35°C) were immersed in a slightly supersaturated solution at 40°C , and prismatic crystals grown at this temperature were introduced in a supersaturated solution at 35°C . In both cases, a progressive change of the morphology could be observed, of the (prismatic \rightarrow elongated) type at 35°C , and (elongated \rightarrow prismatic) at 40°C . These data, illustrated in Fig. 9, confirm that the two described phases are thermodynamically stable in their respective temperature range, below and above 37°C .

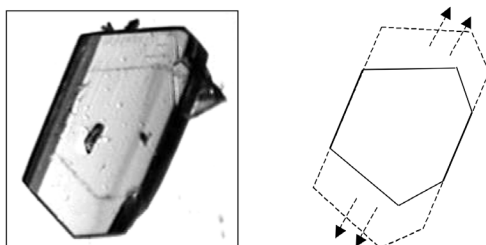


Fig. 9 Optical microscopy photograph and schematic representation showing the morphological evolution of a single crystal of $\text{TM}\alpha\text{-CD}/(S)\text{-PE}$ initially obtained at 40°C and subsequently immersed in a supersaturated solution at 35°C

Conclusions

Despite important structural similarities, the existence of distinct crystalline phases in the quaternary system ($\text{TM}\alpha\text{-CD}/(S)\text{-PE}/(R)\text{-PE}/\text{water}$) could be established, and the determination of their solubility curves in the temperature range $30\text{--}55^\circ\text{C}$ revealed that the $\text{TM}\alpha\text{-CD}/(R)\text{-PE}$ complex is at least two times more soluble than the supramolecular complexes formed with $(S)\text{-PE}$ between 35 and 45°C .

Although these solubility differences cannot be easily understood from a structural point of view, they allow to account for the possibility to separate the two enantiomers of PE by means of successive crystallizations. Our results also indicate that the chiral resolution process is not hindered by the existence of a complete solid solution between the two anhydrous diastereomeric compounds.

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