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DEHYDRATION MECHANISM AND CRYSTALLISATION BEHAVIOUR OF LACTOSE

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Abstract

The dehydration mechanism of α-lactose monohydrate was investigated by several techniques and interpreted on the basis of structural data. Whatever the dehydration conditions (heating or use of hygroscopic organic solvents), the departure of water molecules occurs cooperatively in channels parallel to the c axis of the initial structure. Subsequently, the reorganization leads to the closest packing (hygroscopic metastable form, $L\alpha_H$) under heating or to the stable anhydrous form ($L\alpha_S$), probably via a nucleation and growth process in ethanol. The use of acetone as dehydrating solvent on single crystals of α-lactose monohydrate led to the unexpected formation of single crystals of the anomeric β-lactose at room temperature, from which the crystal structure of β-lactose could be accurately redetermined. Recrystallization experiments of anhydrous lactose allowed to prepare N-methylpyrrolidinone and DMSO solvates of α-lactose.

Keywords: crystal structure, dehydration mechanism, lactose, solvates, whiskers

Introduction

Most of the academic and industrial research groups working in the field of pharmaceutical research and development have now recognised the importance of detecting polymorphic forms and solvated varieties at the earliest stage of development of potential new drugs [1–4], in connection with the associated differences in terms of physical properties and behaviours (stability, morphology, solubility, dissolution rate, size distribution, mechanical properties, processing, etc.) [5–7]. It is also admitted that the existence of such crystalline and distinct varieties of a same compound is a widely spread phenomenon among organic compounds since about one third of them is assumed to exhibit polymorphism and another third is supposed to exist as solvates [8].

In this context, elaborating more rational approaches and proposing efficient strategies for the research of new polymorphs and solvates become major issues for the optimi-

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sation of research and development procedures. For instance, Byrn *et al.* [9] have contributed to these efforts by means of decision trees designed to treat gradually the useful questions associated to polymorphism, existence of solvates and presence of amorphous forms. Another important contribution is that initiated by Dunitz and Bernstein in their paper entitled 'Disappearing polymorphs' [10], followed by other papers in the same area [11–13]. In the initial paper, the rate of formation of critical nuclei for a given form, as well as the importance of 'finding the right experimental conditions' were underlined and clearly identified as key notions. A third approach of interest in the field of polymorphism is made of various attempts designed to predict *ab initio* the potential polymorphic forms of a molecule by means of computational and modelling tools [14–16]. Despite the obvious interest of these developments, the associated methodologies cannot provide any information regarding the preparative routes of possible crystalline forms of interest. Nevertheless, some important progress results from the possibility to consider the case of solvates and of several distinct molecules (with different conformations) in the asymmetric unit [17].

As a possible original way to discover new polymorphs (or solvates) of a given molecular compound, the methodology presented and applied in the present paper is derived from a unified model devoted to the dehydration mechanism of molecular crystals [18], and consists in using the existence of hydrates or solvates in order to promote the formation of new molecular packings by means of suitable dehydration or desolvation conditions. The simplified representation presented in Fig. 1 illustrates the fact that, starting from a hydrated structure, the use of 'hard' dehydration condi-

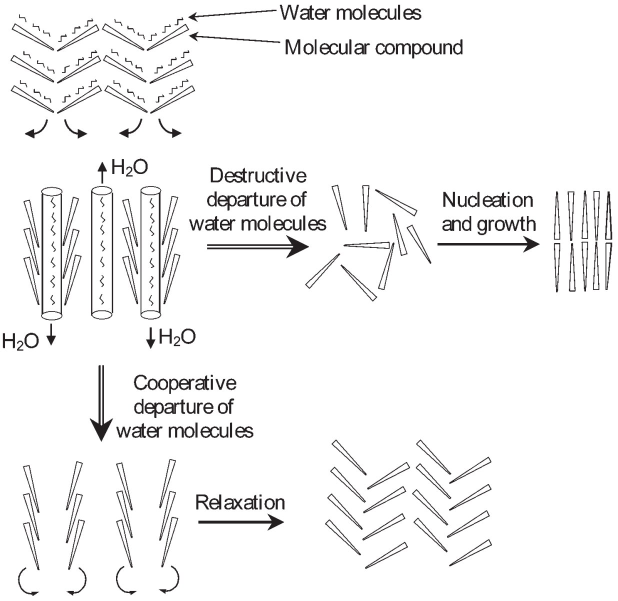
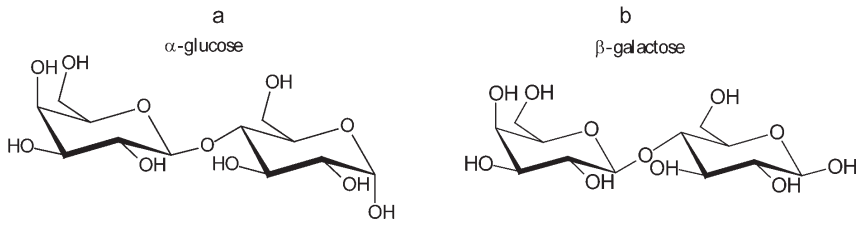


Fig. 1 Simplified representation of the methodology allowing the research of new polymorphic forms on the basis of different dehydration mechanisms

tions is likely to produce an amorphous material, which can in turn evolve towards an anhydrous variety by means of a nucleation and growth mechanism. On the contrary, smooth dehydration conditions can, in some cases, allow a cooperative departure of water molecules, followed by a structural reorganization step leading to the nearest possible crystalline packing. This type of mechanism is therefore characterized by the persistence, during the dehydration process, of similar molecular contacts in the whole sample, in connection with the occurrence of continuous and cooperative molecular movements. Moreover, the resulting packing is, at least to a certain extent, determined by the initial hydrated structure, so a part of the structural information is preserved, whereas the critical step for destructive-reconstructive mechanisms is likely to be the nucleation of the anhydrous variety, and the structural information is lost during such processes.

Hence, it appears that modifying the experimental dehydration (or desolvation) conditions can induce the formation of two different polymorphs, and this kind of methodology can be used for different solvates of a given compound, which gives rise, at least theoretically, to the possibility of preparing a number of new polymorphic forms. In our paper presenting the model of dehydration mechanisms [18], it was also highlighted that a complete elucidation and a detailed understanding of dehydration processes is more likely to be reached from a combination of different experimental techniques associated with structural data and the use of molecular modelling tools. As far as possible, crystal structures of both the initial and the final solid varieties should be determined.


a α-glucose

b β-galactose

Fig. 2 Structural formulae of α-glucose (a) and β-galactose (b)

The present paper reports the application of these ideas in the case of a famous and widely used excipient, α-lactose monohydrate (Lα-H_2O hereafter, Fig. 2a) [19]. The underlying aims are connected to (i) a better understanding of its dehydration behaviour under various conditions; (ii) the access to new structural data for anhydrous varieties, and possibly (iii) the preparation of new anhydrous or solvated crystalline forms of α-lactose.

Numerous studies have been devoted to the crystallization and dehydration behaviours of Lα-H_2O [20–28] as well as to the crystallization of anhydrous α-lactose in various solvents [29, 30]. Although some contradictory results have sometimes been obtained, in particular regarding the identification of anhydrous forms [28], it is well established that two dehydrated forms can be prepared from Lα-H_2O: a hygroscopic form, Lα_H, usually obtained by heating in *vacuo* the monohydrate above 100°C during a few hours, and a more stable anhydrous form, Lα_S, resulting from dehydration in dry hygroscopic solvents (methanol, ethanol, acetone, etc.) or obtained by heating Lα-H_2O at more than 120°C in suitable conditions [20]. The crystal structure of Lα-H_2O was first described in 1971 [31, 32] and accurately redetermined in 1984 [33]. The second anomeric form, β-lactose (Lβ hereafter, Fig. 2b), is known only as an anhydrous form and can be crystallized in water at temperatures higher than 93.5°C [20]. Nevertheless, rapid mutarotation in aqueous medium induces that Lβ represents about 60% of dissolved lactose at room temperature [34].

Experimental section

In consistency with the methodology presented above, the dehydration behaviour of Lα-H_2O was investigated under various conditions and using several techniques. This diversity allowed to study the dehydration towards Lα_H, the conditions for the formation of Lα_S, and also the possible transformation of α-lactose into β-lactose in the solid state or by using specific dehydration conditions.

Preparation of samples and crystallizations

Commercial Lα-H_2O was purchased from Acros (99.5%) and was first purified in toluene (suspension at about 5–10% mass/mass maintained under mechanical stirring at room temperature for at least 24 h) in order to eliminate a crystalline impurity [19, 34] detected by X-ray powder diffraction (XRPD) at $2\theta=18°$. The sample was then slowly recrystallized in water at room temperature, and only gentle grinding was applied after drying in order to avoid partial amorphization. Anhydrous Lα_H could be prepared, according to the procedure of Buma and Wiegers [20], by heating powdered Lα-H_2O in a non covered petri dish at 110°C during at least 6 h, and was maintained for a period not longer than 30 min under P_2O_5 atmosphere before analysis in order to avoid partial rehydration. The stable anhydrous Lα_S form was obtained by dehydration of a Lα-H_2O suspension in ethanol.

Crystallization experiments in dimethylsulfoxide (DMSO), N-methylpyrrolidinone (NMP), dimethylacetamide (DMAc), 1,3-dimethyl-2-imidazolidinone (DMI) and 1,1,3,3-tetramethylurea (TMU) were carried out according to the following procedure. Due to the low vapour pressure of these solvents in ambient conditions, finely ground Lα_S was dissolved at 60°C under stirring until saturation was reached. The suspension was then filtered on a glass filter (porosity 4) and the saturated solution was slowly cooled down and maintained at 4°C (or –20°C, depending on the melting point of the solvent) until formation of significant quantities of solid. In the case of DMSO, the solubility was too high [23], so a mixture DMSO/ethanol (70/30 *v/v*) was used. When available, the solid sample was submitted to XRPD for identification and comparison with known crystalline forms of lactose.

Thermal analysis

DSC experiments were performed using a Setaram 141 apparatus. Between 25 and 30 mg of the sample was introduced in an aluminium crucible and heated at the 2 K min^{-1} constant rate from 30°C to 200/220°C. DTG measurements were performed with a Setaram PTA92 apparatus, using identical sample and heating rate conditions.

X-ray powder diffraction

Identification of crystalline phases was carried out by means of X-ray powder diffraction (XRPD), with a Siemens D5005 diffractometer equipped with a copper source. For temperature-resolved XRPD, the heating rate was about 1 K min^{-1}, and the recording time for each pattern was about 30 min. All XRPD measurements were carried in ambient atmosphere.

Crystal structure determination

A single crystal of sufficient size and quality was mounted on a Bruker Smart Apex diffractometer equipped with a CCD detector. Unit cell dimensions and integrated intensities were measured at 100 K, with a MoK$_\alpha$ X-ray source. The structure was solved with the direct methods and refined with the SHELX-5.10 program [35].

Results and discussion

Dehydration mechanism of α*-lactose monohydrate*

Dehydration by heating

Figure 3 presents the DSC curves obtained for Lα-H_2O and Lα_H. These curves are in agreement with those published by Figura and Epple [28], although we could observe significant variations when samples were prepared by various routes or treated under different conditions (manuscript in preparation). In the absence of thermal or physical pre-treatment, the dehydration endothermic peak can be unambiguously identified at 133°C (onset temperature). The small exotherm depicted by Figura and Epple at about 170°C is actually preceded by a small endothermic reaction at about 165°C, and fusion/degradation is observed from 210°C upwards. When starting the DSC measurement from room temperature with Lα_H, the successive endo/exotherms appear at 160°C with a larger magnitude.

Temperature-resolved XRPD experiments have been performed between 30 and 180°C. Figure 4 allows to visualize the evolution of XRPD patterns, and to identify the phases by using the d-spacing marks presented below the patterns. Furthermore, comparisons with individual XRPD patterns contained in Fig. 11 can be helpful for identification. From Fig. 4, it can be seen that the pattern characteristic of the monohydrate disappears at about 110°C and is replaced by that of Lα_H. A second change occurs at 160°C, corresponding to a transition between $L\alpha_H$ and $L\alpha_S$. A few peaks of $L\beta$ can also be identified for temperatures higher than 140°C, indicating that mutarotation could occur in disordered intermediate state of the solid state reaction.

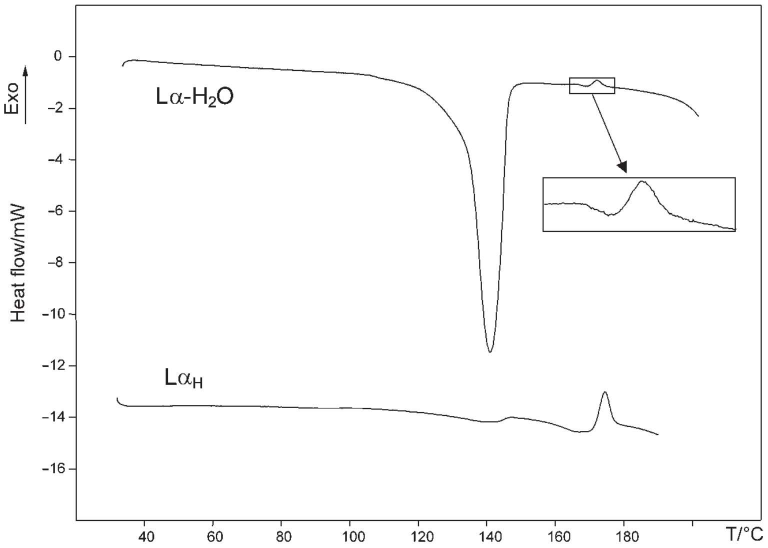


Fig. 3 DSC curves of $L\alpha$-H_2O and $L\alpha_H$ carried out at a heating rate of 2°C min^{-1}

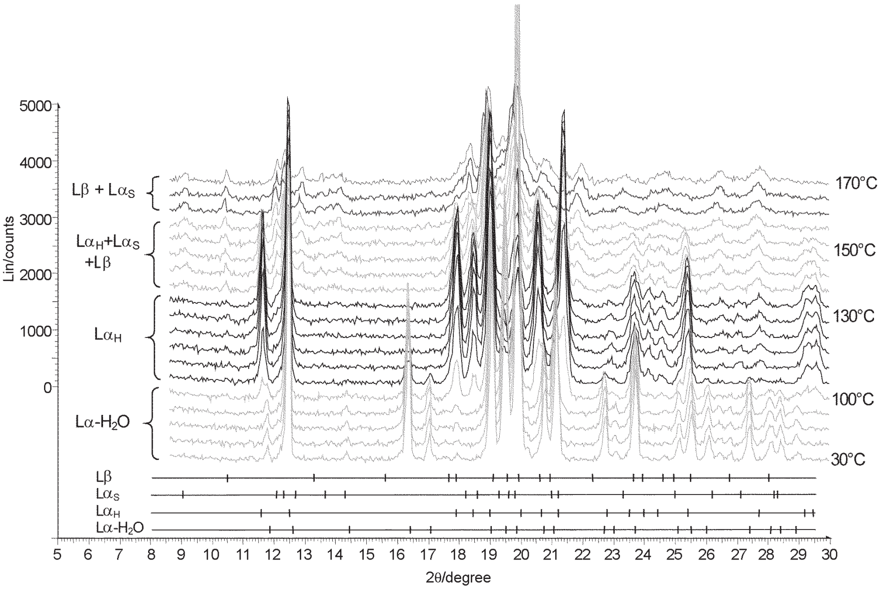


Fig. 4 Temperature-resolved XRPD patterns of $L\alpha$-H_2O between 30 and 180°C

These DSC and XRPD results indicate that dehydration induced by heating leads to the unstable Lα_H form. Further heating induces a polymorphic transition towards the stable anhydrous form Lα_S. Nevertheless, the detailed analysis of the present results reveals some differences, compared to previous interpretations. Indeed, Figura and Epple had found identical XRPD patterns for Lα-H_2O and Lα_H, and had deduced that crystal structures were similar for these forms [28]. In the present study, we have retrieved, for Lα-H_2O and Lα_H, the d-spacing values published by Buma and Wiegers [20], from which nothing can be concluded regarding eventual structural similarities.

Dehydration in ethanol

In order to investigate the dehydration mechanism of Lα-H_2O in details, optical microscopy observations have been performed on single crystals during dehydration induced by a hygroscopic solvent (Fig. 5). It can be seen from these photographs that, after two weeks in ethanol at room temperature, the global shape of the particles is preserved, but different macroscopic effects of dehydration can be depicted on the crystal surfaces. On {1k0} faces, lines or cracks parallel to the c direction are observed and the most developed {0-11} faces become ill-defined. The (010) surface does not seem to be strongly affected by dehydration under these conditions.

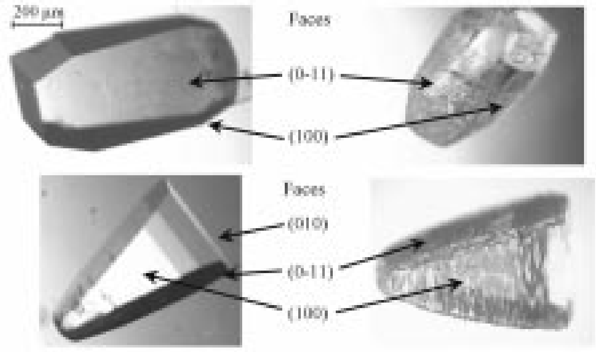


Fig. 5 Optical microscopy photographs presenting the macroscopic effect of dehydration on single crystals of Lα-H_2O (left) after two weeks in ethanol (right)

Although XRPD indicated that the resulting solid is composed of the Lα_S variety, it appears that the observed macroscopic effects associated with dehydration in ethanol give insights mainly on the process of departure of water molecules, corresponding therefore to the transition towards Lα_H. It can be deduced from these observations that dehydration of Lα-H_2O does not occur by means of a strongly destructive mechanism nor by the progressive displacement of a reaction interface [36], but is more likely to proceed in a cooperative and structured way.

Using the crystallographic parameters and atomic coordinates published in [33], projections along a and c axes of the Lα-H_2O crystal structure are presented in Fig. 6,

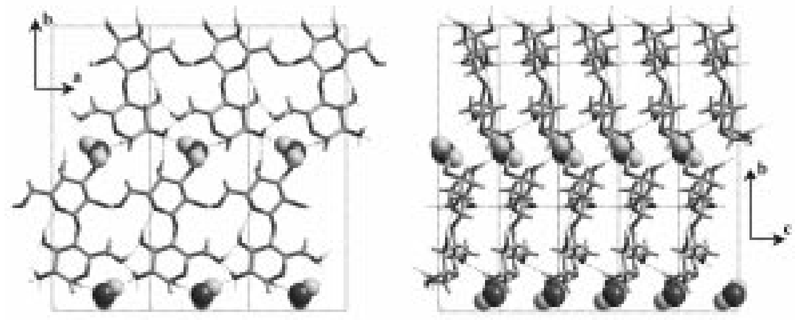


Fig. 6 Projections along a (right) and c (left) axes of the $L\alpha$-H_2O crystal structure

and allow to interpret the optical microscopy observations described above and summarized in Fig. 7. Indeed, water molecules in $L\alpha$-H_2O are located in structural channels parallel to the c direction, which correspond obviously, owing to the complex 3D network of H-bonds, to the easiest departure direction.

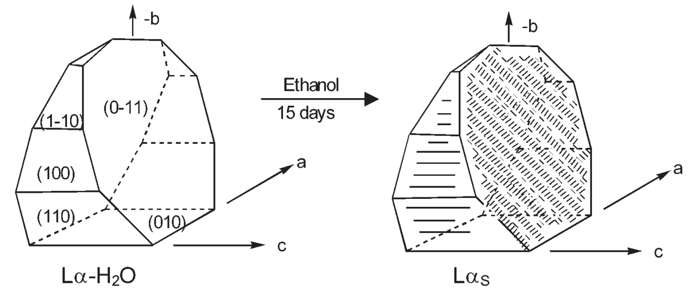


Fig. 7 Summary of the optical microscopy observations carried out during dehydration in ethanol of $L\alpha$-H_2O single crystals, leading to $L\alpha_S$

Due to the role played by these water molecules in the structural cohesion (each water molecule is H-bonded to four different α-lactose molecules), this departure is likely to be accompanied by the formation of crystal defects which, at the macroscopic level, appear as grooves or cracks parallel to the c axis on {1k0} faces. Moreover, the alteration of {0-11} faces can also be explained by the fact that water molecules are evacuated from the crystal through the corresponding surfaces, resulting in numerous defects and possibly in a partial surface dissolution.

SEM observations of dehydrated single crystals (Fig. 8) tend to confirm this interpretation by revealing that (0-11) 'surfaces' are actually made of residual fragments of α-lactose separated by large cracks. Therefore, the particles resulting from dehydration probably consist of lamellar or acicular fragments elongated along the c direction, referred to the unit cell of the monohydrate, and the whole dehydration mechanism is likely to occur by means of a cooperative departure of water molecules, followed by a cooperative reorganization step. This induces that a structural filiation (or a transmission of structural information) is likely to exist between $L\alpha$-H_2O and

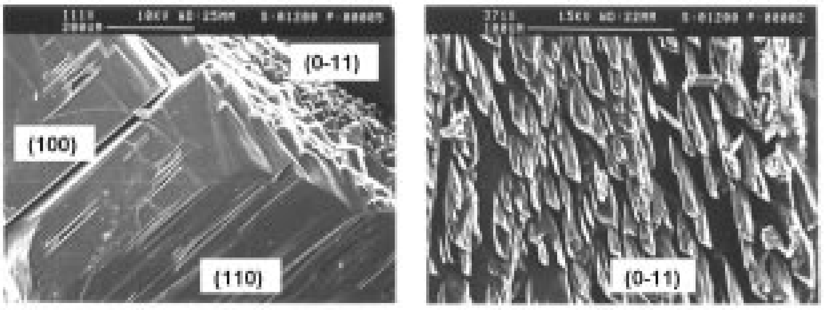


Fig. 8 SEM photographs of $L\alpha_S$ particles showing the effects of dehydration in ethanol on the crystal surfaces of $L\alpha$-H_2O particles

$L\alpha_H$, which could constitute a valuable starting point for the structure determination of $L\alpha_H$ from its XRPD pattern [37–39] or by means of computational methods [40].

Dehydration in methanol and acetone

In 1999, Nordhoff and Ulrich [41] have published a methodology designed to obtain solid phases with high specific surface areas, and involving the dehydration of crystalline hydrates in lower alcohols by means of the formation of 'whisker-like' crystals [42, 43]. It consists in suspending a hydrated phase in a solvent that induces dehydration. The miscibility of water with the organic solvent, on the one hand, and the very low solubility of the substance in this solvent, on the other hand, lead to a dendritic growth mechanism, so that 'whisker-like' crystals of a new phase are produced.

A similar methodology was applied to large single crystals of $L\alpha$-H_2O suspended in methanol or acetone at room temperature. In methanol, a large number of very small particles appeared quite rapidly (about 1 h), not only on the surfaces of the initial particle but also at the bottom of the petri dish, as can be seen from Fig. 9a. The total quantity of produced crystals was insufficient for identification by means of XRPD.

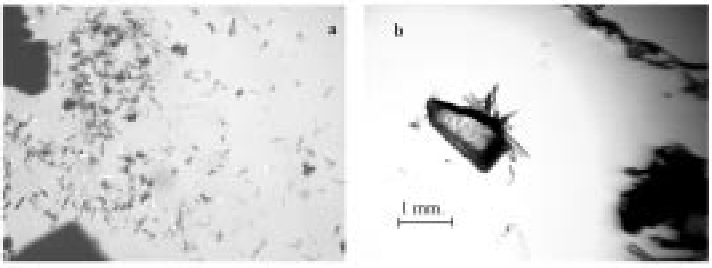


Fig. 9 Optical microscopy photographs showing the formation of 'whisker-like' particles when single crystals of $L\alpha$-H_2O are immersed during 2 weeks in hygroscopic solvents (a – in methanol; b – in acetone)

In acetone, the formation of ‘whisker-like’ crystals was almost limited to the surfaces of the initial particle and occurred slowly, so that large crystals could be isolated and extracted from the growing medium after a few days (Fig. 9b). Unexpectedly, the analysis of these single crystals by means of X-ray diffraction revealed the presence of anhydrous β-lactose (see next section).

Hence, although it is known that suspending Lα-H_2O as a stirred powder in acetone induces its dehydration and the formation of $L\alpha_S$, it appears here that dehydration of Lα-H_2O as single crystals in smooth conditions without stirring leads to Lβ crystals. Since the solubility of α-lactose is very low in acetone, mutarotation cannot be expected in this solvent at room temperature. Therefore, it has to be assumed that, during dehydration in the above conditions, the departure of water molecules is accompanied by a partial dissolution and solvation of α-lactose molecules. These solvated molecules have to be surrounded by water in such a way that mutarotation can occur before diffusion of water in acetone. When a sufficient quantity of β-lactose molecules is formed, the nucleation and growth of Lβ crystals can occur in the vicinity of the initial Lα-H_2O particles. This complex mechanism requires that diffusion must be as low as possible, which explains why Lβ is not obtained from a stirred suspension of Lα-H_2O in acetone. The fact that large Lβ crystals were produced instead of the expected $L\alpha_S$ indicates that nucleation and growth of this form is hindered in these conditions whereas growth of Lβ is favoured.

Crystal structure redetermination of anhydrous β-lactose

Structural analysis was performed using a single crystal of Lβ prepared according to the procedure detailed above. Table 1 summarizes the main measurement conditions and the crystallographic parameters. For comparison, unit cell dimensions found in the first structure determination of Lα [44] are included. Crystallographic data and fractional coordinates have been deposited at the Cambridge Crystallographic Data Center (CSD) and registered under the deposition number CCDC 165495.

Table 1 Measurement conditions and crystallographic parameters for the Lβ crystal structure

Formula	$C_{12}H_{22}O_{11}$		(This work)	(From [44])
Molecular mass	342.3 g mol^{-1}	Temperature	100 K	298 K
Scan type	2θ	Space group	monoclinic $P2_1$	monoclinic $P2_1$
Dx	1.612 g cm^{-3}	*Z*	2	2
Wavelength	0.71073 Å	*a*	4.9325 (4) Å	4.954 (5) Å
F (000)	364	*b*	13.2700 (11) Å	13.349 (6) Å
θ limit	50.05°	*c*	10.7792 (9) Å	10.839 (6) Å
Nb of measured reflexions	6385	β	91.554 (4) °	91.31 (9) °
		V	705.29 Å^3	716.7 Å^3
Nb of independant reflexions	2484	μ	14 cm^{-1}	/
		R / *Rw*	5.8% / 10.4%	6.8% / –
Nb of observed reflexions	1868			

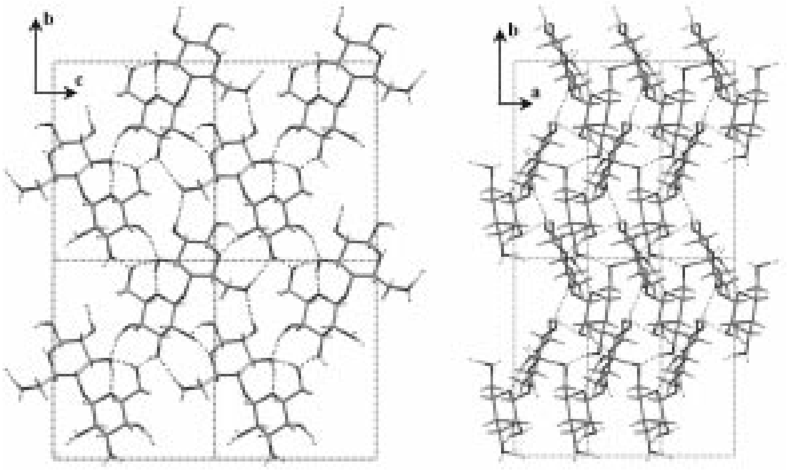


Fig. 10 Projections along c (right) and a (left) axes of the Lβ crystal structure

Systematic comparisons of bond lengths and angles, as well as conformational superimpositions revealed only limited geometry differences between the former structure and the present work. The complex hydrogen bond network was fully retrieved and can be contemplated from Fig. 10. Each β-lactose molecule is involved in one intramolecular H-bond and 14 intermolecular H-bonds with 8 neighbouring molecules.

Superimposition of the experimental XRPD pattern with that calculated from the crystal structure allowed to confirm that this structure is representative of powder samples (data not shown). Morphological predictions carried out with the geometric Bravais–Friedel–Donnay–Harker (BFDH) model [45] led to theoretical crystal habits elongated along the a direction, in consistency with the unit cell dimensions. Thus Lβ single crystals shown in Fig. 9b are likely to be elongated along this a direction.

Crystallization of anhydrous α-lactose from organic solvents

Understanding more accurately the dehydration mechanism of Lα-H_2O towards anhydrous α-lactose and the polymorphic transition between these anhydrous forms ($L\alpha_H \rightarrow L\alpha_S$) would require further structural information regarding these anhydrous varieties of α-lactose. We have therefore carried out a series of recrystallization attempts, using as starting material the stable $L\alpha_S$ form. The very poor solubility of α-lactose in usual organic solvents induced that only 5 solvents were able to dissolve significant quantities of $L\alpha_S$ and could be used for crystallization attempts: dimethyl sulfoxide (DMSO), N-methylpyrrolidinone (NMP), dimethylacetamide (DMAc), 1,3-dimethyl-2-imidazolidinone (DMI) and 1,1,3,3-tetramethylurea (TMU).

Although no large single crystals of $L\alpha_S$ could be prepared up to now, it was observed in the case of NMP and DMSO/ethanol mixture that new XRPD patterns were obtained, as shown in Fig. 11. Gravimetric, DSC and NMR-H^1 analyses revealed that the corresponding solids are new solvates of α-lactose. It could be established in the

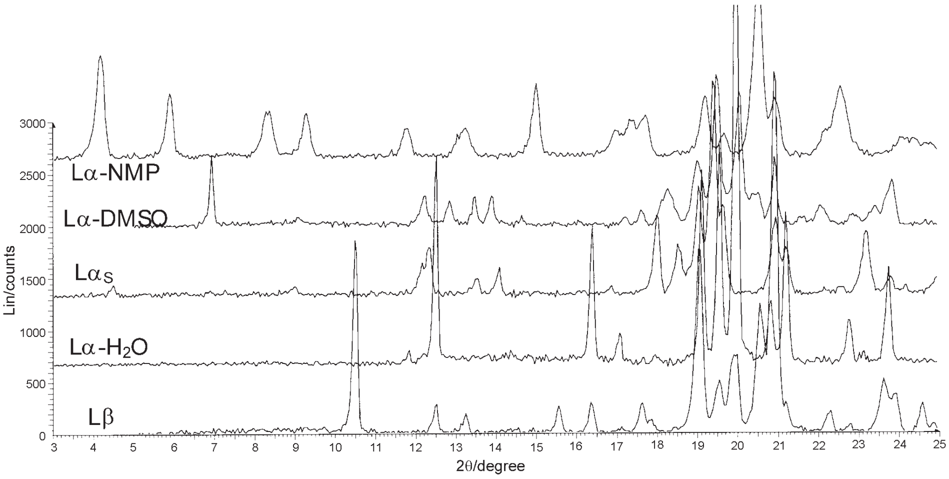


Fig. 11 XRPD patterns of the new solvates of α-lactose with NMP and DMSO, and comparison with those of known forms of lactose

case of NMP that the stoichiometry of the solvate is (1:1). The DSC and DTG curves of this compound, obtained with the same heating rate (2°C min^{-1}), are presented in Fig. 12. The peak observed at 68°C (onset temperature) from DSC is in a shape of an invariant and is therefore likely to correspond to a peritectic decomposition of the solvate, accompanied by a partial loss of NMP. This non-congruent fusion of the solvate is followed (onset about 80°C) by the progressive dissolution of the Lα$_S$ crys-

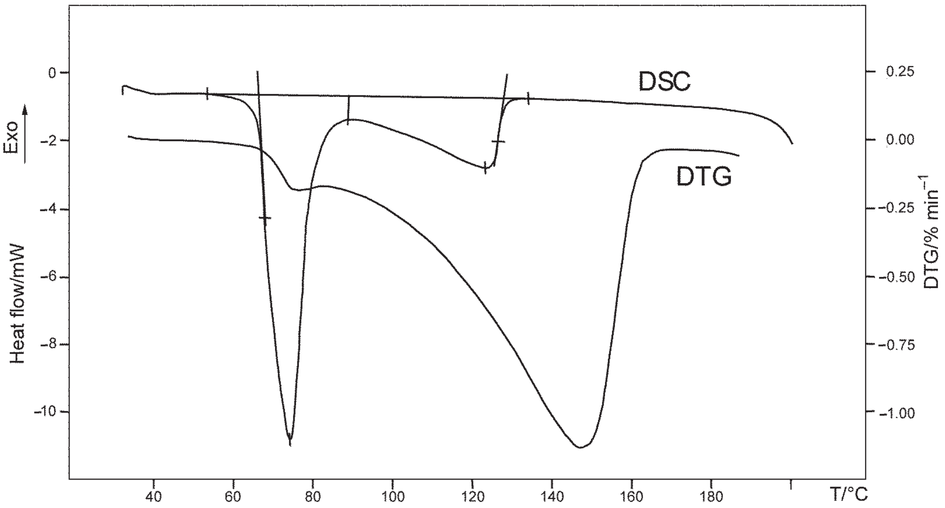


Fig. 12 DSC and DTG curves for the NMP solvate of α-lactose (heating rate: 2°C min^{-1})

tals formed, combined with a mass loss indicating the progressive evaporation of NMP up to 150°C. This low stability of the NMP solvate is confirmed by the fact that, under atmospheric conditions, this compound undergoes a slow transformation towards Lα-H_2O (about 5% after 8 days and full transformation after one month). Furthermore, temperature-resolved XRPD measurements indicated that $L\alpha_S$ is obtained after desolvation, i.e., as soon as the temperature is higher than 80°C.

Conclusions

The present study illustrates that the understanding of the dehydration mechanism of molecular hydrates requires detailed and accurate investigations, using a combination of complementary techniques associated with structural data. It could be established that a key step of the dehydration process of α-lactose monohydrate is the cooperative departure of water molecules along structural channels parallel to the crystallographic c direction. When dehydration is induced by heating, the reorganization of the anhydrous material results in the formation of the hygroscopic $L\alpha_H$ variety. Further heating is required to induce the polymorphic transformation towards the stable anhydrous $L\alpha_S$ form. In a dehydrating solvent such as ethanol, $L\alpha_S$ is produced but optical microscopy allows to assess a similar dehydration mechanism, according to the macroscopic effects induced by dehydration on crystal surfaces. Our results indicate that the crystal structure of the $L\alpha_H$ variety could probably be determined by means of computational techniques combined with accurate XRPD data. Single crystals of the $L\alpha_S$ variety could not be prepared from recrystallization attempts but these experiments led to the formation and the partial characterization of at least two original solvates of α-lactose. Surprisingly, dehydration of single crystals in acetone without stirring led to the preparation of single crystals of anhydrous β-lactose, and to perform an accurate structure redetermination of this variety. Further investigations are in progress in order to access to new structural data, to study the influence of various physical parameters on the thermal behaviour of Lα-H_2O, and to improve the characterization of the new solvates.

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