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Understanding the Role of Water in 1,10-Phenanthroline Monohydrate

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Abstract

The solid forms emerging from an experimental screening programme of 1,10-phenanthroline (*o*-phen), a heavily used bidentate ligand, and interconversion pathways of its two neat forms, the monohydrate (**Hy1**) and four solvates with acetone, chloroform, dichloromethane and 1,2-dichloroethane are described. The solvates, identified and characterised with thermoanalytical methods, are unstable when removed from the mother liquor and desolvate at room temperature depending on the relative humidity (RH) to anhydrate I° (**AH I°**) or transform to **Hy1**. At ambient conditions **Hy1**, a stoichiometric channel hydrate, is the thermodynamically most stable *o*-phen solid form. The enthalpically stabilised **Hy1** melts at 102 °C or dehydrates to **AH I°** at RH < 10% at 25 °C. The potential energy difference between **Hy1** and **AH I°** was calculated to be approx. 15 kJ mol⁻¹. The second anhydrate polymorph (**AH II**) can be obtained from the quench cooled melt of *o*-phen, but is unstable at ambient conditions and transforms within minutes to either **AH I°** or **Hy1**. The two neat polymorphs are enantiotropically related and water-free *o*-phen transforms to **Hy1** at RH > 16%. The structural and stability features of the solid forms, in particular **Hy1**, are unravelled by a combination of experimental (thermal analysis, moisture sorption/desorption and storage experiments, infrared spectroscopy and powder X-ray diffraction) and computational modelling (crystal structure prediction and lattice energy calculations), providing a consistent picture why *o*-phen forms a very stable Z' = 3 channel hydrate.

1 Introduction

The interaction of water molecules with solids is a critical issue in the development of many industrial materials and products as the presence of water is difficult to avoid during production, handling and storage processes. The water in such production steps may originate from different sources such as solvents, excipients or from atmospheric humidity. Absorption or adsorption of water molecules can profoundly affect a products performance with regard to its physical and chemical stability, powder flow properties, wettability, dissolution properties, compressibility, etc. 1–4 A term commonly used for highlighting the propensity of a material to interact with water is ‘hygroscopicity’, 5–7 roughly quantifying the amount of water vapour, at a given RH and temperature, that is taken up by a solid by means of non-covalent interactions.

Small organic molecules, such as drug compounds and other fine chemicals, often incorporate water into their structure to form hydrates, which can exist in different polymorphic forms⁸ (e.g. a polymorphic monohydrate) and/or different hydration states (monohydrate, dihydrate etc.).⁹ Among drug substances hydrates are rather common (> 30%)^{10–12} and have attracted increasing attention in pharmaceutical industry for their potential impact on the development and performance of (drug) products.¹³ Such water adducts are frequently formed by compounds with excess hydrogen bond acceptors and/or mismatch of H-bonding donor and acceptor groups. Many hydrates show a well-defined stoichiometric relationship between the water and the host molecule, termed ‘stoichiometric hydrates’.¹⁴ Here the water mostly plays a crucial role in stabilising the structure and upon dehydration a distinct solid form is obtained. The water held in another class of hydrates (non-stoichiometric hydrates) can be removed by humidity and/or temperature changes in a non-stoichiometric fashion without the occurrence of phase changes, with the dehydration product being isostructural with its parent phase. The lattice of the latter hydrate class may expand continuously over a wide range to accommodate water, although the structures are still isomorphous.¹⁵ As water egress and ingress is determined by the environmental RH/temperature conditions, a non-stoichiometric behaviour presents some problematic issues for formulations, such as weighing. One of the main factors affecting the stability of hydrates is the role of the water molecule in the intermolecular network of the crystal structure.¹⁶ Therefore, unravelling hydrate formation from a structural point may help us in making hydrates and their stability more predictable.

In this study we have chosen *o*-phenanthroline (*o*-phen or 1,10-phen) as a model compound for studying structural reasons for hydrate formation. The molecule is used in the fields of analytical, organic, bioorganic, supramolecular coordination and catalysis chemistry as a versatile starting material due its geometric and chemical properties (rigidity, planarity, aromaticity, basicity and chelating capability).^{17, 18}

Because it forms strong complexes with many metal ions the compound is heavily used in coordination chemistry, for example as ligands for catalysis,¹⁹ as a stabilizing agents for nanoparticle synthesis,²⁰ and activator in organic synthesis.²¹ Other promising technological and medical applications are for example in the field of electroluminescent materials,^{22, 23} organic light-emitting devices (OLED),²⁴ organic semiconductors,²⁵ or as chemical therapeutic agents due to the ability of 1,10-phenanthroline to bind or interact with DNA.²⁶ To date numerous X-ray crystallographic studies of the *o*-phen and many of its metal complexes were undertaken. Already in 1974 Sen reported lattice dimensions and space group ($P31m$) of *o*-phen hydrate (CSD-Refcode²⁷: ZZZAMS01).²⁸ This publication triggered a heavy debate about the “true” space group. Donnay et. al also suggested $P31m$ as the most probable space group,²⁹ but Nishigaki et. al came to the conclusion that the hydrate crystallises in $P3_1$ or the enantiomorphous space group $P3_2$ (ZZZAMS02).³⁰ The first complete single crystal structure of the hydrate including atomic coordinates for *o*-phen and water oxygen, was published in 1995 ($P3_1$, ZZZAMS03), with the remark that the hydrate structure is a displacive modulation of an idealised $P3_1$ parent structure.³¹ Since then, four additional full structure determinations have been published (ZZZAMS04 – $P3_1$,³² ZZZAMS05 – $P3_1$,³³ ZZZAMS06 – $P3_2$ and ZZZAMS07 – $P3_2$).³⁴ Nelyubina et al. ³⁴ reinvestigated the monohydrate structure and revealed a partial twinning by a twofold

rotation about direction $[2\ 1\ 0]$ corresponding to the crystallographic twofold symmetry axis of $P3_212$, which was previously assumed to be the parent group of α -phen hydrate. The crystal structure of anhydrous α -phen has been solved in 1977 (OPENAN).³⁵ The hygroscopic single crystals were obtained by sublimation in vacuum and belong to the monoclinic space group $C2$, with one α -phen molecule being located at a general position and the second one at a special position with crystallographic symmetry 2. The third crystallographically characterised α -phen solid form is a chloroform monosolvate (CAMZIA).³⁶

Despite being a heavily used compound hardly any information on solid forms, stability and interrelations of the forms can be found in the literature. Proell³⁷ briefly investigated the monohydrate of α -phen in his PhD thesis using thermo-analytical methods (hot-stage microscopy and differential scanning calorimetry). In 1987 Riedmann³⁸ reinvestigated the compound, providing spectroscopic and thermo-analytical data and reporting the existence of a second polymorphic form of the anhydrate.

The present work seeks to establish the reason for hydrate formation for α -phen, to explain why the monohydrate is very stable and finally, why a $Z' = 3$ hydrate is formed. A broad range of complementary analytical techniques was applied to resolve the structural and stability features of the solid forms emerging from a polymorphism screen, including hot-stage microscopy (HSM), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), infrared spectroscopy, powder X-ray diffraction (PXRD) and gravimetric moisture sorption/desorption experiments. The computational work, crystal structure prediction (CSP) seeks to establish the stability of the monohydrate and anhydrate I° (**AH I**) relative to other putative $Z' = 1$ monohydrate structures. Hence, we provide a rather comprehensive picture of the solid state forms of α -phen comprising seven forms, two anhydrides, the monohydrate and four solvates, a variety of new thermo-analytical as well as moisture dependent stability data and the results of lattice energy calculations.

2 Experimental

2.1 Materials, Solid Form Screening Experiments

1,10-Phenanthroline monohydrate (**Hy1**) was purchased from Merck (lot 438 1 326825) and used as obtained. The organic solvents used were all of analytical grade and purchased from Aldrich or Fluka.

The solid form screen encompassed RT (room temperature) solvent evaporation, solvent cooling crystallisation, melt crystallisation, sublimation and moisture sorption/desorption studies. For more details, see ESI† section 2.

AH I was prepared either by heating a ground **Hy1** sample to 105 °C for 15 min or storing **Hy1** over a desiccant (P_2O_5) at 25 °C for a week. The second anhydrate, **AH II**, was obtained in < 1 mg quantities by annealing the melt of **AH I** at RT.

The four solvates (acetone, chloroform, dichloromethane and 1,2-dichloroethane) were obtained in solvent cooling crystallisation experiments. Saturated solutions of α -phen were

prepared close to the boiling point of the respective solvent, followed by filtration of the solution and slow cooling to RT. The solvate crystals were stable in the mother liquor.

2.2 Thermal Analysis

Hot-stage Microscopy (HSM)—For HSM investigations a Reichert Thermovar polarisation microscope, equipped with a Kofler hot-stage (Reichert, A), was used. Photographs were taken with an Olympus DP71 digital camera (Olympus, D).

Differential Scanning Calorimetry (DSC)—DSC thermograms were recorded on a DSC 7 or Diamond DSC (Perkin-Elmer Norwalk, Ct., USA) controlled by the Pyris 7.0 software. Using a UM3 ultramicrobalance (Mettler, Greifensee, CH), samples of approximately 2 - 5 mg were weighed into perforated/sealed aluminium pans. The samples were heated using rates starting from 0.5 to and 20 °C min⁻¹, with dry nitrogen as the purge gas (purge: 20 ml min⁻¹). The two instruments were calibrated for temperature with pure benzophenone (mp 48.0 °C) and caffeine (236.2 °C), and the energy calibration was performed with indium (mp 156.6 °C, heat of fusion 28.45 J g⁻¹). The errors on the stated temperatures (extrapolated onset temperatures) and enthalpy values were calculated at the 95% confidence intervals (CI) and are based on at least three measurements.

Thermogravimetric Analysis (TGA)—TGA was carried out with a TGA7 system (Perkin-Elmer, Norwalk, CT, USA) using the Pyris 2.0 software. Approximately 3 - 5 mg of sample was weighed into a platinum pan. Two-point calibration of the temperature was performed with ferromagnetic materials (Alumel and Ni, Curie-point standards, Perkin-Elmer). Heating rates starting from 0.5 to 10 °C min⁻¹ were applied and dry nitrogen was used as purge gas (sample purge: 20 mL min⁻¹, balance purge: 40 mL min⁻¹).

2.3 Gravimetric Moisture Sorption/Desorption Experiments

Manual water desorption studies were performed at 25 °C over a desiccant (P₂O₅) providing a relative humidity (RH) of 0%. The loss of water as a function of time was determined gravimetrically³⁹ with a below-weighting balance (AT 250 semimicro balance, Mettler Instrumente AG, Greifensee, CH). The sample mass used in these studies was about 300 mg.

Automated gravimetric moisture sorption and desorption studies were performed with the multisample gravimetric moisture sorption analyzer SPS11-10μ (ProUmid, Ulm, D). Approximately 200 mg of **Hy1** were used for the investigations. The measurement cycle was started at 90% with an initial desorption cycle (decreasing humidity) to 0%, followed by a sorption cycle to 95% relative humidity (RH). The RH changes were set to 2% for all cycles (except for the last step: 90% to 95% in one step), the equilibrium condition for each step was set to a mass constancy of ± 0.001% over 60 minutes.

2.4 Powder X-ray Diffraction

The PXRD patterns were obtained using an X'Pert PRO diffractometer (PANalytical, Almelo, The Netherlands) equipped with a θ/θ coupled goniometer in transmission geometry, programmable XYZ stage with well plate holder, Cu-K α _{1,2} radiation source and a solid state PIXcel detector. The patterns were recorded at a tube voltage of 40 kV, tube

current of 40 mA, applying a step size of $2\theta = 0.013^\circ$ with 80 s or 200 s per step in the 2θ range between 2° and 40° . For non-ambient RH measurements, a VGI stage (VGI 2000M, Middlesex, UK) was used.

2.5 Computational Modelling

Hypothetical crystal structures of *o*-phen monohydrate ($Z' = 1$), starting from the PBE0/6-31G(d,p) optimised molecular conformation calculated using Gaussian09,⁴⁰ were generated with the program CrystalPredictor.^{41–43} 300,000 structures were generated randomly in 48 space groups ($P1$, $\bar{P}1$, $P2_1$, $P2_1/c$, $P2_12_12$, $P2_12_12_1$, $Pna2_1$, $Pca2_1$, $Pbca$, $Pbcn$, $C2/c$, Cc , $C2$, Pc , Cm , $P2_1/m$, $C2/m$, $P2/c$, $C222_1$, $Pmn2_1$, $Fdd2$, $Pnna$, $Pccn$, $Pbcm$, $Pnnm$, $Pmmm$, $Pnma$, $P4_1$, $P4_3$, $\bar{A}$, $P4/n$, $P4_2/n$, $I4/m$, $I4_1/a$, $P41212$, $P4_3212$, $P3_1$, $P3_2$, $R3$, $P\bar{3}$, $R\bar{3}$, $P3_121$, $P322_1$, $R3c$, $R\bar{3}c$, $P6_1$, $P6_3$, $P6_3/m$), keeping the molecular geometry rigid. The structures were relaxed to a local minimum in the intermolecular lattice energy, calculated from the FIT44 exp-6 repulsion-dispersion potential and atomic charges which had been fitted to electrostatic potential around the PBE0/6-31G(d,p) charge density using the CHELPG scheme.⁴⁵ The energies of all structures within 13.4 kJ mol^{-1} of the global monohydrate lattice energy minimum were refined (10,000 structures), using DMACRYS⁴⁶ with a more realistic, distributed multipole model⁴⁷ for the electrostatic forces which had been derived using GDMA²⁴⁸ to analyse the PBE0/6-31G(d,p) charge density. Finally, the most stable hydrates (91 structures, 15 kJ mol^{-1} with respect to the most stable) were optimised with periodic density functional calculations (CASTEP⁴⁹). The Perdew-Burke-Ernzerhof (PBE) generalised gradient approximation (GGA) exchange-correlation density functional⁵⁰ and ultrasoft pseudopotentials,⁵¹ with the addition of either the Tkatchenko and Scheffler (TS)⁵² or Grimme (D2)⁵³ semi-empirical dispersion correction, were applied. For more details, see ESI† section 4.

PIXEL calculations^{54–56} were performed on selected low energy monohydrates (PBE-TS optimised structures) to estimate the repulsive (E_R), dispersion (E_D), electrostatic (Coulombic, E_C) and polarization (E_p) contributions from individual pairs of molecules within a crystal. An electron density map was calculated on a three-dimensional grid with a step size of $0.08 \text{ \AA}$ at the MP2/6-31G(d,p) level using GAUSSIAN09 and a PIXEL condensation factor of 4 was applied. For more details, see ESI† section 7.

Structural comparisons were made using the Packing similarity tool in the Solid Form module of Mercury to determine the root mean square deviation of the non-hydrogen atoms in a cluster of n molecules (rmsd_n).⁵⁷

3 Results and discussion

3.1 Crystallisation Experiments

A solvent evaporation screen from 24 solvents resulted in all experiments, except one, in the known monohydrate (**Hy1**). Evaporation from a saturated (25°C) chloroform solution lead to the already structurally characterised chloroform monosolvate.³⁶ However, the presence of opaque crystals indicated that a part of the crystallisation products transformed already to **Hy1**. In crystallisation batches obtained from acetone, dichloromethane and 1,2-

dichloroethane this ‘pseudomorphosis’ (transformed crystals appear opaque due to a transformation, maintaining the outer shape of the original crystals) was completed. Therefore, additional cooling crystallisation experiments were performed (ESI†, Table S3), resulting in three new solvates. These solvates are very unstable at ambient conditions and a transformation to **Hy1** can be observed within seconds after removal from the mother liquor. In contrast, the chloroform solvate is more stable than the three other solvates but within 72 hours this solvate also transforms completely into **Hy1** at approx. 20% RH and 25 °C. Exemplarily for all solvates, the desolvation is shown for the chloroform solvate in Fig. 2. On heating, the solvate crystals turn opaque due to the pseudomorphosis, which is typical for stoichiometric solvates. The desolvation starts at 30 °C, with the maximum desolvation rate occurring at 50 to 60 °C. Desolvation is indicated by the appearance of “dark” spots on the crystal surface, which indicate the nucleation centres of **AH I°**. The number of nucleation centres, starting from the edges and crystal defects, increases with temperature. By embedding the solvates into high viscosity silicon oils, the formation of bubbles was observed, confirming the presence of the solvent of crystallisation.

The supercooled melt of anhydrous *o*-phen crystallises spontaneously to fibrous or platy crystals of **AH II**. Upon heating to > 35 °C or leaving the microscopic melt film preparation for less than 30 minutes at room temperature (dry conditions) a solid-solid transformation of **AH II** to **AH I°** is observed (Fig. 3), as indicated by the appearance of colourful crystals in polarised light microscopy. Upon further heating strong sublimation occurs and the crystals of **AH I°** melt at 118 °C.

Monitoring the **AH II** to **AH I°** phase transformation in DSC experiments proved to be difficult, as (i) in the Al pans **AH I°** nucleates predominantly instead of **AH II** and (ii) the presence of moisture (water) in the DSC pan resulted in the formation of **Hy1**. By crystallising anhydrous *o*-phen on glass or mylar-foil it was possible to prepare phase pure **AH II** and to measure an endothermic phase transformation with DSC at a temperature < 60 °C (ESI†, Figure S1). The observed endothermic phase transition from II to I° proves unequivocally that the two forms are enantiotropically related⁵⁸ with **AH II** being the low temperature form and **AH I°** the stable form at and above room temperature. Cooling DSC experiments, starting with **AH I°**, from room temperature to –120 °C, did not show a phase transformation, suggesting that the I° to II phase transition underlies a strong kinetic control.

3.2 Temperature Dependent Stability of Hy1

Hy1 crystallises in the form of plates or pyramidal crystals. The hydrate is stable at room temperature, but with hot-stage microscopy a rather peculiar thermal behaviour can be observed, particularly in larger crystals. The hydrate crystals turn opaque on the surface on heating above 50 °C due to the phase transformation to **AH I°** (Fig. 4a-d). Dehydration of the **Hy1** crystals stops after an outer layer of **AH I°** has been formed, which acts as a “shield” preventing the hydrate water to egress from the inner regions of the crystals. This mixed phase of **AH I°** and **Hy1** shows eutectic melting at 93 °C (Fig. 4f-g). Upon further heating, the remaining hydrate crystals dissolve in the eutectic melt until the last **Hy1** traces melt and a kind of “capsule” is formed consisting of a water containing liquid in the core

and an anhydrous crystalline “shell” which melts at about 118 °C on further heating. By embedding **Hy1** into high viscosity silicon oil it is possible to determine the melting point of the phase pure hydrate at 101-102 °C (Fig. 4i-l).

The DSC and TGA thermograms were recorded using two distinct **Hy1** batches, differing in particle size: bigger crystals (50 to 250 µm) and smaller crystals (< 40 µm). Furthermore, the influence of the heating rate and the atmospheric condition in a DSC pan (5-pinhole, 3-pinhole and closed) was investigated. Starting with the bigger crystals, each TGA curve shows a two-step dehydration process (Fig. 5a). From RT to 92 °C a slow but steady mass loss is observed. Above the eutectic temperature (93 °C) the remaining water is released faster. The slower the heating rate the more water is released below the eutectic temperature. However, even with a heating rate of 0.5 °C min⁻¹ it was not possible to dehydrate the hydrate crystals prior the eutectic temperature between the hydrate and anhydrate. The TGA curves of the smaller crystals (heating rates 1 to 10) also show a two-step process, albeit the steps are shifted to lower temperatures (Fig. 5b) compared to Fig. 5a. By increasing the surface area of **Hy1** the dehydration under N₂ purge is faster compared to the rate observed for the bigger crystals. Water egress is fast till the surface of the particles is transformed to **AH I**, which then decelerates the dehydration process. With a heating rate of 2 °C min⁻¹ it is possible to complete the dehydration reaction before the eutectic temperature between **AH I** and **Hy1** is reached.

In contrast to the open TGA pans, the DSC crucibles were covered with three- or five-pinhole lids or hermetically sealed, to modify the dehydration rate via the atmospheric conditions in the sample pan. Using the bigger hydrate crystals, pinhole lids and heating rates in the range from 0.5 to 10 °C min⁻¹ (Fig. 5a) clearly shows the eutectic between **AH I** and **Hy1** at 92.3 ± 0.1 °C. Prior to the eutectic temperature dehydration can be seen as small broad endotherm in the temperature range from 25 to 55 °C. The melting of **AH I** at 117.8 ± 0.2 °C corresponds to the third endothermic thermal event. The heating rate curve of 10 °C min⁻¹ shows prior to the melting of **AH I** an exothermic event, indicating a partial crystallisation process of **AH I**. The congruent melting of **Hy1** (102.0 ± 0.2 °C) can be measured using sealed DSC crucibles and heating rates 5 °C min⁻¹.

The DSC thermograms of the smaller **Hy1** crystals (Fig. 5b) clearly show the dehydration reaction in the temperature range from 25 to 90 °C. Using a heating rate of 0.5 °C min⁻¹, five-pinhole lids and a particle size of < 40 µm allows the dehydration reaction to be completed before the eutectic temperature is reached. All other DSC curves in Fig. 5b show the eutectic melting as an endothermic peak at 93 °C. Thus, dehydration of **Hy1** at mild conditions requires a small particle size, otherwise the dehydration reaction will decrease considerably due to the shielding effect of **AH I** formed on the surface of the **Hy1** crystals.

3.3 Gravimetric Moisture Sorption/Desorption Experiments

The moisture sorption/desorption experiments of *o*-phen (Fig. 6a) show that **Hy1** is stable over a wide relative humidity (RH) range at 25 °C, i.e. no desorption is observed in the RH range starting from 10% to 95%.

On decreasing the humidity at 25 °C, the dehydration occurs when the RH is less than 10%. The dehydration product, **AH I**^o (Fig. 6b), is only stable at RH values < 18%. At moisture conditions of 18% and higher, the **AH I**^o takes up water, and the transformation to **Hy1** occurs within less than 12 hours. In contrast, the dehydration reaction is slower and takes approx. 4 days (< 8% RH). The distinct steps and hysteresis between the desorption and sorption isotherms are characteristic for a stoichiometric hydrate, but the hysteresis is small compared to other systems, e.g. β -resorcylic acid.⁵⁹ The critical water activity (thermodynamic transition point) for the system **AH I**^o $\leftrightarrow$ **Hy1** lies in between > 0.08 and < 0.18, corresponding to a RH of 18% > x < 8% at 25 °C. Based on the measured data it can be concluded that **Hy1** is a very stable hydrate, it releases its water only at low RH and conversely **AH I**^o is a rather unstable solid form, which absorbs water at RH values that are below ambient storage conditions (30 to 60 % RH). This information is crucial for handling and storing anhydrous α -phen.

3.4 Monohydrate Crystal Structure and Computationally Generated Monohydrates

α -phen crystallises in the trigonal space group $P3_1$ (or enantiomorphous space group $P3_2$) with each three α -phen and three water molecules in the asymmetric unit ($Z' = 3$). The three α -phen molecules have the appropriate relationship $x, y, z, x + 1/3, y - 1/3, z, x - 1/3, y - 2/3, z$. The structure can be described in terms of three pseudo-equivalent chains which run parallel to the crystallographic c axis (Fig. 7). The water molecules form infinite H-bonded O–H $\cdots$ O C(2)₆₀ water chains and each water molecule forms an additional H-bond to α -phen, O–H $\cdots$ N, graph set motif D(2). Thus, the water molecule shows the water environment type DDA61 and the maximum number of possible strong intermolecular interactions for a α -phen monohydrate is present. In two out of the three 3_1 (or 3_2) screw-chain H-bonded motifs the water molecules point into the same direction (viewed along c). In the third screw-chain the directionality of the chain is turned upside-down. The monohydrate structure can be classified as a channel hydrate.

To investigate the possible packing arrangements of α -phen and water in hydrate structures and unravel the structural role of water in α -phen we computed the $Z' = 1$ monohydrate crystal energy landscape. The $Z' = 1$ crystal energy landscape was complemented with the experimental **Hy1** structure, optimised using the same settings as described in section 2.1 and ESI† section 4. The experimental **Hy1** structure was found as lowest energy structure in Fig. 8a, 1.96 kJ mol^{−1} more stable than the lowest energy $Z' = 1$ monohydrate. Thirteen monohydrate packings were calculated to be within 8 kJ mol^{−1} of **Hy1** (labelled in Fig. 8a). As expected, the addition of the water molecule to α -phen leads to the formation of strong intermolecular O–H $\cdots$ O and O–H $\cdots$ N interactions. In the majority of the lowest energy structures the water molecules show the water environment type DDA, the water molecules acting twice as H-bonding donor and once as H-bonding acceptor, as seen in **Hy1**. Each one acceptor and one donor group is interacting with adjacent water molecules and α -phen and water molecules are interlinked via an O–H $\cdots$ N hydrogen bond. In all, except one DDA structure the water molecules form C(2) chains as seen in the experimental hydrate. The higher symmetric, tetrameric structure $I4_1/a(12)$ has the water molecules arranged in a tetramer (Fig. 8b). Furthermore, in all computed DDA structures only one of the α -phen nitrogen is involved in hydrogen bonding. The higher energy structures (> 7.31 kJ mol^{−1}

with respect to **Hy1**) show the water environment type DD, with water molecules bridging two *o*-phen molecules, $N\cdots H-O-H\cdots N$, leading either to *o*-phen-water chains or tetrameric ring motifs. Only two high energy structures show a H-bonded dimer ring between *o*-phen and water. In all DD structures both *o*-phen nitrogen atoms are acting as acceptor group and water does not form any strong intermolecular interactions with other water molecules. In addition to the classical H-bonding interactions also $C-H\cdots N(O)$, $C-H\cdots \pi$, and $\pi\cdots\pi$ interactions contribute to the lattice energy of the hydrate structures (Table 1). The packing indices for all structures on Fig. 8a range from 71.1% to 76.8%, thus, the hydrates are dense structures. **Hy1** has a packing index of 73.3% and **AH I°** a packing index of 73.9% (PBE-TS structures).

The CSD-Materials tool Hydrate Analyser was used to estimate the space of the computationally generated hydrate structures occupied by water molecules. In the DDA water-chain structures (Fig. 8b) at least 9.6% of the space is occupied by water molecules. In contrast, in the tetrameric structure (12, DDA) only 7.4% of the space is occupied by water. Depending on the water bonding motif the DD water bridge structures (Fig. 8b) can be sub-classified. In the DD water chain hydrates the water molecules tend to occupy slightly more space than in the tetrameric DD water ring motif structures. The two water-phen ring hydrates, isolated site hydrates, show the lowest water space occupancies of 4.2% and 4.8%, respectively. Based on the lattice energy estimations the DDA water chains are the preferred H-bonding interactions in *o*-phen monohydrate structures.

To estimate the strength of the intermolecular interactions in *o*-phen we calculated the pairwise intermolecular interaction energies in **AH I°**, **Hy1** and selected lowest-energy $Z' = 1$ monohydrate structures (2 - DDA, 7 - DD and 8 - DDA, Table 1). The two chosen DDA hydrate structures differ in that in structure 2 the water chain is mediated by 2_1 symmetry and in structure 8 by 3_1 (3_2) as in **Hy1**. In the **AH I°** structure ($Z' = 2$ used for the calculations) the strongest pairwise interaction was calculated to be 28.7 kJ mol^{-1} between the two symmetry independent molecules, with dispersion forces being the strongest contributor to the energy (and lattice energy in general). The introduction of water molecules in the hydrate structures allows the formation of strong hydrogen bonds. In the DDA chain structures the strongest pairwise intermolecular interaction involves the $O-H\cdots N$ H-bond, contributing pair-wise approx. 40 kJ mol^{-1} to the intermolecular lattice energy. The contribution of the water $\cdots$ water interactions is calculated to be up to 23.6 kJ mol^{-1} . In both types of interactions (phen $\cdots$ water and water $\cdots$ water) the electrostatic contribution is responsible for the high strength of the interactions. The energy of the strongest phen $\cdots$ phen close contact is of similar magnitude in the DDA hydrates as in **AH I°**. In the DD hydrate the two strong phen $\cdots$ water interactions are weaker than the phen $\cdots$ water interaction in DDA hydrates, but this is compensated for that two phen $\cdots$ water interactions can be formed in DD hydrate structures. The crystal PIXEL energies, corresponding to the intermolecular energy and roughly to the lattice energy as *o*-phen may be treated as a rigid body molecule, calculated structure 7 ($-181.8 \text{ kJ mol}^{-1}$) as slightly more stable than the two DDA structures ($-178.6 \text{ kJ mol}^{-1}$ for both structures). Based on the fact that the pairwise phen $\cdots$ water interactions are stronger than the phen $\cdots$ phen interactions the strong tendency towards hydrate formation, as derived from the sorption data (Fig. 6a), can be rationalised.

Packing similarity comparisons between **Hy1** (Fig. 9a) and the computed low-energy structures in Fig. 8a revealed isostructurality between **Hy1**, 3 and 8, if water molecules are ignored (Fig. 9b&c). The rmsd_{30} values (α -phen only) for each possible pair of structures were calculated as follows: **Hy1** and 3 – 0.871 Å, **Hy1** and 8 – 0.573 Å, and 3 and 8 – 0.679 Å. Thus, the α -phen packing of the low energy $Z' = 1$ structures 3 and 8 corresponds to the **Hy1** packing (framework). In three of the four full **Hy1** structure determinations (ZZZAMS05-07) the water H-atoms and thus the N-atom involved in the O–H...N hydrogen bonds are superimposable, however, in structure ZZZAMS04 all three water chains point towards the same direction along c . Thus, the other N-atom is involved in H-bonding. Structure optimisations (DFT-D) starting from both structure models indicated that the ZZZAMS05-07 water proton positions are more stable than the orientations seen in ZZZAMS04 and therefore the more stable packing was used for the comparisons/structure discussion. The two matching (α -phen) computed $Z' = 1$ hydrate framework structures 3 and 8 differ solely in the directionality of the water chain along the c axis (Fig. 9b&c). Structure 3 has the **Hy1** 3_1 screw-chain H-bonded water motif, denoted as type 1 in Fig. 9d&e. In structure 8, the water chain (but not the entire water-phen 3_1 screw-chain) is orientated upside-down (Fig. 9f).

Based on the lattice energy calculations the $Z' = 3$ structure was calculated, independent of the used dispersion correction (TS and D2), to be more stable than the corresponding $Z' = 1$ monohydrate framework structures. Structure 3 was calculated to be +4.54 kJ mol⁻¹ and +3.87 kJ mol⁻¹ less stable at PBE-TS and PBE-D2, respectively; structure 8 +5.11 kJ mol⁻¹ (PBE-TS) and +5.81 kJ mol⁻¹ (PBE-D2) less stable than the experimental structure. Thus, the energetic stabilisation of the $Z' = 3$ structure seems to be the driving force for the formation of the $Z' > 1$ monohydrate.

3.5 Entropic Stabilisation of Hy1 and Stoichiometric vs. Non-stoichiometric Dehydration Mechanism

The gravimetric moisture sorption/desorption isotherms indicate that **Hy1** is a very stable hydrate and that water-free α -phen is very hygroscopic. Computationally, we can estimate the stability of a hydrate relative to its anhydrate by comparing the lattice energy of the hydrate ($E_{\text{latt-Hy}}$) to the lattice energies of the anhydrate ($E_{\text{latt-AH}}$) and ice ($E_{\text{latt-ICE}}$). If $E_{\text{latt-Hy}} < E_{\text{latt-AH}} + E_{\text{latt-ICE}}$ (we assume that hydrate formation is thermodynamically driven), then the hydrate is more stable than the anhydrate. In other words, a lower (more negative) value indicates higher stability. Using the lattice energies of **Hy1**, **AH I°** (Table 2) and a value of –59 kJ mol⁻¹ 62, 63 for ice (the used functional is known to overbind the ice crystal structures^{64, 65}) a potential energy difference ($-U_{\text{Elatt}}$) of –13.49 kJ mol⁻¹ (PBE-TS) to –16.39 kJ mol⁻¹ (PBE-D2) was calculated. These results not only confirm that hydrate formation is driven by a greater potential energy of the hydrate but also that the monohydrate is a stable phase (phase transition values of ca. 15 kJ mol⁻¹, $-U_{\text{Elatt}} \sim H_{\text{trs}}$) and thus reproduce the experimentally derived thermodynamic stability order at ambient conditions, despite the fact that the models neglect temperature effects.

Lattice energy calculations on **AH I°** and the monohydrate framework structure (**Hy1** without water molecules, **Hydehy**) were performed to rationalise why no non-stoichiometric

dehydration behaviour is observed for **Hy1** upon desorption, despite of the fact that **Hy1** is a channel hydrate. Independent of the used dispersion correction the computationally generated isomorphous hydrate structure was calculated to be less stable than **AH I°** by +9.37 kJ mol⁻¹ (PBE-TS) and +6.21 kJ mol⁻¹ (PBE-D2). The loss of the strongest pair-wise intermolecular interaction upon dehydration (phen...water, Table 1) and the fact that the isomorphous hydrate structure is less stable than the experimental **AH I°** may account for the fast reorganisation (phase transition) of the dehydrated hydrate to **AH I°**. Finally, the comparison of the lattice energy of **Hy1** and **Hy_{dehy}** allowed us to estimate the contribution of the water molecules (phen...water and water...water interactions) to the hydrate lattice energy to be approx. 82 kJ mol⁻¹.

4 Discussion

Despite being a heavily used compound new solvates were found for *o*-phen in the experimental solid form screen and for the first time the temperature- and moisture-dependent stability and interrelation pathways between the solid forms were established (Fig. 10).

Combining the experimental findings with computational modelling allowed us to unravel not only the reason for hydrate formation of *o*-phen but also rationalise the high stability of its monohydrate and the reason for the formation of a *Z'* = 3 hydrate structure. Only at low RH values (< 10% RH) at 25 °C does water-free *o*-phen become more stable than the hydrate. The high stability of the hydrate complicated the finding and characterisation of the other solid forms.

4.1 Can we Rationalise why *o*-phen Forms a Hydrate and Labile Solvates?

The fact that *o*-phen lacks H-bonding donor groups, but has two strong H-bonding acceptor groups has to be seen as the driving force for hydrate formation. The argument, as seen for other compounds, e.g. 4-aminoquinoline, that in addition to the imbalance of H-bonding donor and H-bonding acceptor groups, also the packing efficiency may be a driving force for hydrate formation does not hold for *o*-phen, as the packing index for the anhydrous form (**AH I°**: 73.9%) was calculated to be slightly higher than for the hydrate (73.3%). *o*-Phen molecules can form densely packed structures, with dispersion forces contributing significantly to the lattice energy (Table 1) and thus to the stability of the water-free crystal form.

The lack of H-bonding donor groups may also indicate that other solvate forms exist for *o*-phen. Interestingly, all of the yet found and characterised solvate forms do not have strong H-bonding donor groups. Acetone, dichloromethane, 1,2-dichloroethane and chloroform may interact with the *o*-phen through weak C-H...N close contacts, as seen in the chloroform solvate (CAMZIA36). Upon exposure to water vapour a fast exchange of the chloroform layers with water is observed, rationalising that the chloroform molecule is only weakly bound. One may expect that other, especially lower alcohol molecules form solvates with *o*-phen, but the latter has not been observed yet. Either the right experiments using absolute solvents and excluding moisture from the experiments to avoid the highly competitive water...phen interactions have not been performed yet, or this is simply because

the alcohol molecules are too big to form stable packings with α -phen and/or with itself as seen for the water chains in Fig. 8. The four solvate forms can be best described as transient phases, as they become unstable after removal from the mother liquor. Nevertheless, the existence of labile solvates needs to be known of and considered. Solvates that desolate readily as soon as they are removed from the mother liquor can easily be overlooked in polymorph screening programmes, and wrong conclusions concerning the solvent effects on the nucleation of individual solid forms may result. Several cases have been reported where a solvate can be the only route to a distinct solid form, e.g. Form III of DB7, which needs the dihydrate as (conformational) precursor⁶⁷. Therefore, knowledge of even highly unstable and transient phases is crucial for understanding the formation of a specific solid state form and for developing fine chemical products such as pharmaceuticals.

Overall, hydrate formation may be easily rationalised based on a mismatch of H-bonding donor or acceptor groups or the inability of a molecule to pack densely with itself. The reason for hydrate formation in α -phen is the lack of H-bonding donor groups. This is also true for many other compounds such as neocuproine (2,9-dimethyl-1,10-phenanthroline)^{68–70} and 1,10-phenanthroline HCl⁷¹, for both of which hydrates have been described. Thus, α -phen and derivatives are another class of compounds that are prone to hydration, similar to morphinanes.⁷² On the other hand, rationalising transient or labile solvate (hydrate) formation, where the solvent molecules are only weakly bound may not be straight forward based on the molecular diagram or anhydrate packing only. Often, solvate formation is related to packing frustration, but this argument does not hold for α -phen.

4.2 Channel Hydrate: Stoichiometric vs. Non-stoichiometric Dehydration Behaviour, Stable vs. Unstable Hydrate

The computed monohydrate crystal energy landscape (Fig. 8a) reveals that the water molecules are well accommodated and strongly bound in the hydrate structures. The pairwise intermolecular energy calculations with PIXEL show that the strongest contributions to the hydrate lattice energies involve the water molecules, independent whether DDA or DD water environments are present. We used structure 8, isomorphic $Z' = 1$ hydrate framework structure, as a reference for the experimental $Z' = 3$ hydrate as PXIEL calculations only allow calculations for two molecules in the asymmetric unit and the experimental hydrate contains six molecules. It is interesting that in all of the lowest computed monohydrate structures and the experimental structure the water molecules are arranged in channels. Location of water molecules in open channels, as seen in **Hy1**, often but incorrectly implies the presence of a non-stoichiometric and unstable hydrate form, enabling a fast water egress/ingress depending on the environmental conditions. But by combining the lattice energy calculations and geometrical inspection of the strong H-bonding interactions with PIXEL energy calculations it is evident that the water chains are the backbone of the hydrate structure and essential for its formation and stability. The removal of water from **Hy1** (and related computed structures) destabilises the structure in that no isomorphic dehydrate is observed. Computationally we can generate the isomorphic dehydrate structure, but the packing was calculated to be less stable than **AH I**^o, supporting the experimental observations, i.e. dehydration results in a distinct solid form, **AH I**^o. This is in contrast to the water mobility observed in other channel hydrate structures where water molecules can be

removed in a non-stoichiometric fashion (e.g. brucine HyA73). Thus, the presence of a channel hydrate does not automatically imply that a non-stoichiometric dehydration behaviour can be expected and more importantly that based on the structure alone it is not advisable to derive a possible dehydration mechanism and estimate the stability of a hydrate, unless further analytics/calculations are undertaken.

The simple comparison of the lattice energy of **Hy1** with the lattice energy of **AH I°** and ice allows a quick estimation of the stability of the hydrate relative to its water-free form. In the case of the *o*-phen monohydrates (Fig. 8a) numerous packings are calculated to be more stable than **AH I°**. Furthermore, the packing indices indicate that dense hydrate structures are possible. A potential energy difference of ca. 15 kJ mol⁻¹ for **Hy1** with respect to its dehydration product, the thermodynamically most stable anhydrate form at RT (**AH I°**), agrees with the fact that **Hy1** is a stable hydrate form. This approach can be easily applied for other hydrate systems. However, based on the calculations alone it is not possible to derived moisture- or temperature dependent stability ranges. The latter can only be unravelled by carefully performed experiments.

4.3 Why Does *o*-phen Form a $Z' = 3$ Monohydrate?

Crystal structures with more than one formula unit in the asymmetric unit, $Z' > 1$, have attracted considerable attention in recent years, amongst others, by those interested in CSP and crystal-structure modulation.^{74, 75} Factors leading to higher Z' structures that have been discussed are (i) “awkward” molecular shapes, preventing close packing unless more symmetry independent molecules are present,⁷⁶ (ii) the importance of intermolecular interactions, in particular for monoalcohols and monoamines where steric problems prevent forming H-bonding armaments that exploit both the donor and acceptor capabilities⁷⁷ or (iii) “frustration”, which also involves strong, directional interactions.⁷⁸

o-phen seems to be prone to form structures with $Z' > 1$. The **AH I°** is a $Z' = 1.5$ structure and **Hy1** a $Z' = 3$ structure. None of the three reasons raised for forming $Z' > 1$ structures seem to hold for **Hy1** at a first glance, as isostructural $Z' = 1$ *o*-phen framework packings were found among the lowest-energy structures in the monohydrate crystal energy landscape (Fig. 8a). The molecule does neither exhibit an “awkward” shape nor packing “frustration”. Furthermore, the same strong O–H···N intermolecular interactions between *o*-phen and water can be formed in $Z' = 1$ and $Z' = 3$ hydrate crystals. The reason for the formation of a $Z' = 3$ structure is simple an energetic advantage over the $Z' = 1$ packings. The 3_1 (or 3_2) screw-chain H-bonded water···phen motifs are stable chain packings, but if present in a $Z' = 1$ structure (3 and 8 in Fig. 8a), other *o*-phen···water arrangements can form more stable monohydrate structures. By combining three pseudo-symmetry related 3_1 (or 3_2) screw-chains into one structure the stability in lattice energy is increased by at least –3.9 kJ mol⁻¹ (lower lattice energy) with respect to the related $Z' = 1$ monohydrate structures, due to a better packing arrangement and/or accommodation of screw-chains in **Hy1**. Thus, the $Z' = 3$ structure is more stable than all other calculated $Z' = 1$ monohydrates (Fig. 8a). This highlights that CSP has the ability to explain why a $Z' > 1$ structure may be advantageous over $Z' = 1$ structures and that the statement considering a $Z' > 1$ structure as a crystal “on the way” and thus being metastable is incorrect.⁷⁹

5 Conclusions

Nearly 120 years after the first synthesis of 1,10-phenanthroline by Blau in 1898,⁸⁰ the first systematic study on solid forms and moisture- and temperature dependent interrelation pathways thereof has been undertaken. Out of the seven characterised solid forms, the monohydrate was identified as the only stable form under conditions of relative humidity (RH) typically found during production and storage. The introduction of water molecules enables the formation of H-bonding interactions, explaining the tendency towards the formation of a very stable stoichiometric hydrate, despite the fact that the water molecules are arranged in channels and easily accessible.

The study of the system required the application of a range of different experimental (X-ray diffraction, hot-stage microscopy, differential scanning calorimetry, thermogravimetric analysis and moisture sorption/desorption experiments) and modelling techniques. Crystal structure prediction studies and lattice energy calculations complemented the experimental findings. The calculations give valuable insight into the possible monohydrate packings and together with the experiments they provided the basis for understanding the reason for the formation of a $Z' = 3$ hydrate structure, the stoichiometric dehydration mechanism, and the entropic stabilisation of the hydrate structure with respect to its water-free dehydration product.

The instability of the so far identified solvates of 1,10-phenanthroline means that we cannot exclude the discovery of other labile solvate forms. Nevertheless, the consistency between the experiments and computational techniques used in this study adds confidence that the practically most relevant solid form at production and storage conditions, the monohydrate, has been found and adequately surveyed to avoid complications due to stability and phase interconversions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Molecular diagram of 1,10-phenanthroline (*o*-phen) monohydrate.

Fig. 2.
Photomicrographs of *o*-phen chloroform monosolvate showing the desolvation process in the temperature range 30 °C to 60 °C.

Fig. 3.

Polarised light hot-stage microscopic images of the *o*-phen **AH II** to **AH I°** solid-solid transformation observed at 35 °C. The transformation starts from the (upper) left side.

Fig. 4.

Microphotographs of *o*-phen monohydrate (**Hy1**). (a-d) Dehydration in the temperature range from 30 °C to 90 °C, (e-h) eutectic temperature between **AH I°** and **Hy1** at 93 °C and (i-l) melting of **Hy1** at > 101 °C (crystals embedded in high viscosity silicon oil).

Fig. 5.

TGA and DSC thermograms of α -phen monohydrate using different particles sizes. TGA cures: Hy1(1), Hy1(5) and **Hy1**(10) with numbers in parenthesis corresponding to the heating rate in $^{\circ}\text{C min}^{-1}$. DSC curves: E – eutectic temperature between **AH I** $^{\circ}$ and **Hy1**, Hy1 – melting point **Hy1** and **AH I** – melting point **AH I** $^{\circ}$.

Fig. 6. (a) Gravimetric moisture sorption/desorption isotherms of α -phen **AH I°** $\leftrightarrow$ **Hy1** recorded at 25 °C. (b) Moisture dependent PXRD experiments showing the monohydrate, a mixture of **Hy1** and **AH I°**, and a simulated **AH I°** PXRD pattern (from the single crystal structure OPENAN35). Dotted lines in (b) mark characteristic **Hy1** and **AH I°** peak positions.

Fig. 7.
Packing diagram of *o*-phen **Hy1** (ZZZAMS0734) viewed along the crystallographic *c* axis.
Symmetry independent molecules are coloured differently. H-bonding is indicated with
dotted lines.

Fig. 8.

(a) Crystal energy landscape for *o*-phen monohydrates classified according to water environment type (D – H-bonding donor, A – H-bonding acceptor) and H-bonding motif (chain, etc.). Each symbol in (a) denotes a crystal structure. The experimental $Z' = 3$ structure is encircled and computationally generated $Z' = 1$ structures which are isostructural with 1 (exptl.), ignoring water molecules, are marked with a dotted ellipse (3 and 8). The numbers correspond to the structures stability rank (PBE-D2, ESI† Table S4). The void (water) space was estimated using a 1.0 Å probe radius and a grid spacing of 0.15, ignoring

the water molecules in the hydrate structures using the Hydrate Analyzer tool in Mercury. The vertical line/background separates structures that were calculated to be more stable than **AH I**^o and ice (blue area) from the structures that are less stable (white area).

Fig. 9.

Packing comparisons of **Hy1** (a), computed structures 3 (b) and 8 (c). The void (water) space was estimated using a 1.0 Å probe radius, ignoring the water molecules in the hydrate structures using the Hydrate Analyzer tool in Mercury. The plots (d)-(e) show the 3₁ screw-chain H-bonded motifs.

Fig. 10.

Preparation and transition pathways of the *o*-phen solid forms at different temperatures, relative humidities and solvent crystallisation. **AH I^o** and **AH II** – anhydrous forms, **Hy1** – monohydrate, **S** – solvates. Superscript “o” indicates the thermodynamically stable anhydrate form at RT.

Table 1

PIXEL calculations on o-phen **AH I**^o and selected computationally generated monohydrate structures. Only the most relevant intermolecular interactions for pairs of molecules are listed. For more details, see ESI† section 7.

structure	Interaction ^a	E_C^b	E_P^c	E_D^d	E_R^e	U_{inter}^f
kJ mol ⁻¹						
AH I ^o (<i>Z'</i> =2) <i>C2</i>	A...B (6.913)	-15.7	-7.2	-19.4	13.6	-28.7
	B...B (7.164)	-11.4	-7.7	-19.1	14.9	-23.4
	A...B (6.146)	-6.2	-4.7	-26.3	18.7	-18.5
	A...B (7.539)	-10.1	-4.2	-15.9	14.1	-16.1
	A...B (6.803)	-11.7	-8.1	-20.2	25.1	-15.0
<i>Hy (DDA)</i> <i>2_3064</i> <i>P2₁2₁2₁</i>	A...W (4.231)	-56.3	-25.6	-16.2	59.1	-39.1
	A...A (4.623)	-9.1	-6.3	-54.9	45.4	-25.0
	W...W (2.750)	-54.9	-21.5	-8.3	61.1	-23.6
	A...W (5.848)	-11.0	-2.0	-4.7	4.2	-13.5
	A...W (5.687)	-8.0	-2.7	-5.5	5.6	-10.7
	A...A (7.643)	-4.6	-3.1	-16.2	13.6	-10.3
<i>Hy (DD)</i> <i>7_7249</i> <i>P4₂/n</i>	A...W (4.228)	-47.4	-22.1	-15.0	51.2	-33.2
	A...W (4.111)	-43.3	-20.1	-15.3	48.6	-30.1
	A...A (3.770)	0.1	-6.2	-59.8	41.7	-24.2
	A...A (8.375)	-8.0	-2.5	-11.1	8.3	-13.4
	A...W (5.359)	-12.7	-4.9	-8.6	13.5	-12.7
	A...A (8.505)	-6.2	-2.6	-10.7	8.0	-11.5
<i>Hy (DDA)</i> <i>8_2877</i> <i>P3₂</i>	A...W (4.161)	-63.9	-28.8	-17.2	69.2	-40.6
	A...A (5.788)	-16.4	-7.7	-29.5	29.0	-24.5
	A...A (5.828)	-16.8	-7.6	-29.2	29.2	-24.4
	W...W (2.942)	-32.6	-10.6	-6.2	26.4	-22.8
	A...W (5.848)	-12.0	-2.6	-5.5	6.9	-13.3
	A...A (7.541)	-4.6	-2.0	-15.5	9.4	-12.7
	A...A (7.573)	-4.1	-1.5	-13.2	6.5	-12.4

^aPIXEL energies are for a pair of molecules. The pairs of molecules are defined by the distance between their centers of mass in Å. A and B – symmetry independent o-phen molecules, W – water

^b electrostatic (Coulombic) energy

^c polarisation energy

^d dispersion energy

^e repulsion energy

f total intermolecular energy: $U_{\text{inter}} = E_{\text{C}} + E_{\text{P}} + E_{\text{D}} + E_{\text{R}}$. The non-additivity of E_{P} is not included. DD and DDA describe the water environments (D – H-bonding donor and A – H-bonding acceptor).

Table 2

Lattice energy calculations (E_{latt}) for **Hy1**, **AH I°** and the hydrate framework structure (**Hy1** without water molecules, **Hy_{dehy}**) and potential energy differences for the solid forms **Hy1** and **AH I°**.

method ^a	E_{latt} (Hy1)	E_{latt} (AH I°)	E_{latt} (Hy_{dehy})	U_{Elatt} (Hy1 → AH I°)
kJ mol ⁻¹				
PBE-TS ^b	-207.11	-134.62	-125.25	-13.49
PBE-D2(sp) ^c	-186.11	-110.72	-104.51	-16.39

^a CASTEP relaxations with dispersion correction (k-points: 0.07 Å⁻¹, cut-off: 780 eV)

^b lattice parameters and atomic positions optimised

^c lattice parameters fixed to the PBE-TS lattice parameters and atomic positions optimised.