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Synthonic modelling of quercetin and its hydrates: explaining crystallization behaviour in terms of molecular conformation and crystal packing

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Abstract

Hydrated structures of a specific compound can often have different physiochemical properties compared to the anhydrous form. Therefore, being able to predict and understand these properties, especially the stability, is critical. In this study quercetin, a flavonoid molecule, is modelled in three different states of hydration to gain an understanding of the effect of water molecules on the

structure, packing and conformation energetics of the three forms. Conformational analysis and modelling of intermolecular interactions (synthonic modelling) have been performed. It was found that in the anhydrous form hydrogen bonding is the strongest type of interaction while in the two hydrate structures, the incorporation of water within the lattice leads to the formation of hydrogen bonds between the quercetin and water molecules. Within hydrates quercetin molecules adopt a more planar conformation which allows them to pack more closely by strong π-π stacking interactions, thus resulting in a higher relative stability. The modelling results highlight the importance of water in the stabilization of the lattice and explain the preferential nucleation of the dihydrate form. It is further demonstrated how synthonic modelling can be a predictive tool for the product's properties, leading to more efficient product design and faster development.

1. Introduction

Hydrates are multicomponent crystalline solids that contain both the host molecule and one or more water molecules incorporated in the crystal lattice,[1] whereby it is thought that approximately a third of organic compounds can form hydrated structures.[2] Understanding organic molecules propensity to form hydrates and mapping their thermodynamic stability is of critical importance when formulating particulate products, particularly for the pharmaceutical, food and agrochemical industries.[3]

Exposing anhydrous structures to conditions of high relative humidity can induce hydration, whilst some hydrates precipitate in water or aqueous solutions, after the dissolution of the formulated product in the desired media (stomach or digestive tract for drugs, wet soil for agrochemicals).[4] Since hydrates can present significantly different physical and chemical properties (solubility, density, bioavailability etc.) compared to their anhydrous counterparts, their unexpected formation can dramatically affect the quality and efficiency of a particulate product. [5-

[7] In some cases the hydrated forms of molecular crystals exhibit properties that are desired for a particulate product, for example improved release rate or higher stability.[3,7-9] Understanding how the water interacts with the host molecules in crystalline solids, as well as how the pathway from solution to hydrated structure can become preferential over the pathway to pure form, is essential to predict the relative stability and crystallisability of hydrated crystal forms.[1]

Different crystal forms, whether they are single or multi component, can vary in terms of molecular conformation or crystal packing.[10] The presence of water molecules within a crystal lattice can affect the type and strength of intermolecular interactions within the bulk, which in turn could stabilise molecular conformations that may not be accessible within the pure crystal forms.[11] This in turn not only can influence the properties of the solid-state, but also the kinetic pathway from the solution to the crystalline state.

Unsatisfied hydrogen bond donors and acceptors within an anhydrous crystal structure, those that could potentially form hydrogen bonds, is the main driving force for hydrate formation. [9,12] The incorporation of water molecules in the crystal lattice provides additional H-bond donor and acceptor sites that can potentially compensate for the unsatisfied hydrogen bonding between the donors and acceptors of the host molecule.[6,9,12] In 1991 Desiraju reported that hydrate formation is more favourable when the hydrogen bond donor/acceptor ratio (d/a ratio) for the host molecule is low, and usually <0.5.[13] The d/a ratio is a ratio between the hydrogen bond donors acceptors that could potentially participate in a hydrogen bond, and represents a measure of the imbalance between the two in the structure.[13] The incorporation of water molecules within the crystal structure increases the number of available bond donors and shifts the donor/acceptor ratio towards unity.[14] The polarity of the functional groups of the molecules or atoms that form a crystalline structure can also influence hydrate formation, as compounds with charged or polar groups or

atoms have a high tendency to form hydrated structures.[1] Finally, the formation of hydrates tends to decrease the void space in a crystal structure and leads to more efficient packing.[9,15]

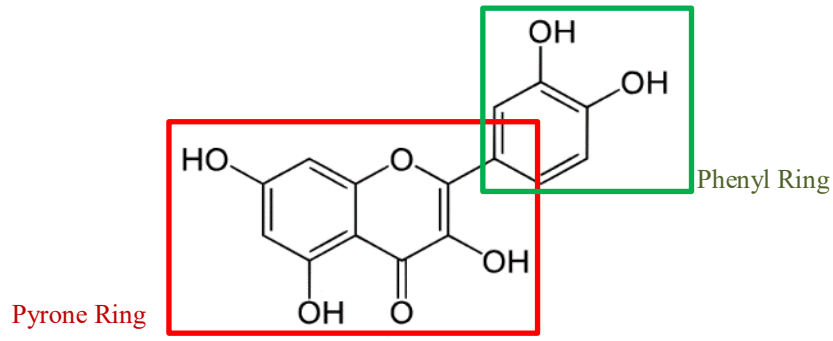


Figure 1. The molecular structure of quercetin

In this work, quercetin, 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one, is chosen as the model compound. The molecule is a polyphenolic compound found in many fruits and vegetables, including onions, tomatoes, apples and berries.[16-18] Due to this vast range of biological effects, having antioxidant, anti-inflammatory, anti-bacterial and anti-hypertensive properties as well as the ability to inhibit the growth of human cancer cell lines, quercetin finds use in the nutraceutical industry and as food supplement or ingredient.[19-25]

The molecular structure of quercetin can be observed in Figure 1.[17, 26-28] Quercetin can exist as anhydrous (QA), monohydrate (QMH) and dihydrate (QDH) forms.[8,16,27,29,30] It is sparingly soluble in water, which results in difficulties when crystallizing the hydrated forms from aqueous solvents.

While the crystal structure of QDH was solved in the late 80s, crystals of QA and QMH of suitable size and quality have not been obtained to be solved by single crystal X-ray diffraction (SCXRD).[16, 30-32] The existence of the QA form was confirmed using several experimental

techniques such as powder X-Ray diffraction (PXRD) and nuclear magnetic resonance (NMR), while for QMH the PXRD pattern was determined in 2011 by Domagata et al. [8,31,32]

Experimental characterisation of the physiochemical properties and thermal stability of the quercetin hydrates has been conducted by Borghetti et al., employing a range of experimental techniques including variable temperature PXRD (VTPXRD), differential scanning calorimetry coupled with thermogravimetric analysis (DSC/TGA) and scanning electron microscopy (SEM). The authors have identified QDH as the most thermodynamically stable form.[33] A study on the solubilities of QA and QDH by Srinivas et al. has shown the aqueous solubility of QA up to 100°C to be higher than that of QDH, implying that QDH is a more stable crystal structure at those conditions.[17] While experimental studies could be laborious, time consuming and expensive, molecular modelling can provide an alternative route to gain insight into the properties and propensity of formation of hydrates, minimizing the required laboratory work needed.[34-37]

Synthonic modelling and computational methods can utilize atomistic force fields drawn from empirical data, to calculate the strength, directionality and dispersive nature of the intermolecular interactions (synthons) within a crystalline structure. This information can help in predicting the physiochemical properties of crystals.[34-36] In the past synthonic modelling has been used to study crystalline structures and estimate their properties, by calculating the lattice energy and identifying the dominant intermolecular interactions.[38-54]

Synthonic modelling allows studying more complex multi-component systems, including those of hydrated structures.[55-57] Characterisation and comparison of the bulk intermolecular interactions within the anhydrous and hydrated structures of a specific compound can provide evidence on how water molecules can affect the intermolecular interactions among the different forms, and direct properties such as crystal shape, thermodynamic stability and surface chemistry. As an example,

Clydesdale et al. (1995) have used synthonic modelling to simulate the morphology of the α-lactose monohydrate crystal structure and identified that the water molecules in the structure play a space-filling role during the growth process.[56] More recently, D.E. Braun et al. have studied the intermolecular interactions in 1,10-phenanthroline anhydrate and monohydrate, and explained the higher stability of the monohydrate form, identifying the lack of hydrogen bond donor groups of the molecule as the reason leading to hydrate formation.[57]

The structure and conformation of the quercetin molecules in the three forms have been studied individually both by experimental and theoretical techniques, and the effect of water on the molecular geometry of quercetin in the hydrated structures has been discussed.[28,58] However, it is still unclear from these studies what is the effect of water on intermolecular packing energetics and conformational energy[59,60] of each structure and how this link to the experimentally observed physiochemical properties of each form, including thermodynamic stability, crystallization behaviour of the compound and the preferential nucleation one hydrated form over the other.

In the presented work, the effect of water molecules on the structure, packing energetics and conformation of a multi-component system characterised by a model molecule, quercetin, and water in different ratios is investigated using a multi-angle modelling approach. Synthonic modelling is used here to compare the type and strength of intermolecular interactions in the structures of a compound at different levels of hydration. A systematic procedure is developed to gain insight of hydrate formation of quercetin and its hydrates, and to explain the crystallization behaviour of the compound. This proposed modelling methodology can be extremely valuable when designing products, processes and storage conditions for particulate products with known hydrates. [61,62]

The intermolecular interactions in the solid state of quercetin and two of its hydrated crystalline forms have been estimated and studied in this work. The knowledge of such interactions can elucidate the different mechanisms of crystal growth for these structures and explain the crystallization behaviour in different solvents, particularly water. Additionally, comparing the main intermolecular interactions can explain differences in the properties (e.g., relative stability and solubility) of crystals structures of the same compound at different hydration levels.

2. Computational Modelling Methodology

2.1 Structure file preparation and minimisation

The crystallographic information files (.cif) for the three quercetin structures were obtained from the Cambridge Structural Database (CDS): quercetin anhydrous (REFCODE: NAFZEC), quercetin monohydrate (REFCODE: AKIJEK), quercetin dihydrate (REFCODE: FEFBEX). [8,16,27]

The crystal structures were minimised using the Forcite module in Materials Studio 2017.[63,64] The torsion angle around the phenyl and pyrone rings of the quercetin molecule was kept rigid while the hydroxyl group torsion angles were allowed to obtain the most energetically favourable configuration according to the packing of each structure. The unit cell parameters were kept constant. The SMART algorithm was selected for the structural minimisation and the DREIDING forcefield was used as this is one of the most suitable force-fields for treating organic molecules[65-68] and it was proved to work effectively with quercetin, as shown in Supporting Information.

The files were exported as .car files (Cartesian coordinates) and then converted to fractional coordinates.

2.2 Conformational Analysis

The quantum chemical calculations were carried out in Gaussian09.[69] The cartesian coordinates of the quercetin molecules from the anhydrous, monohydrate and dihydrate crystal structures were extracted and used as the starting point for the geometry optimization. The energy of the molecules was calculated at the density functional level of theory, utilising the triple zeta with polarisation (TZVP) basis set of Alrich and co-workers.[70] The exchange correlation energy was calculated using the Becke three parameter Lee Yang Parr (B3LYP) functional, with the Grimme D3 dispersion energy function added to account for any intra- or inter-molecular dispersion energy.[71] The aqueous environment was simulated using the conducting polarisable continuum model (CPCM).[72]

To represent the crystal conformer in solution, the central torsion was frozen using the redundant coordinate option, whilst the rest of the molecule was relaxed to reduce any possible energetic inconsistencies due to bond lengths from the crystal structures. To calculate the favoured conformation of each crystal structure conformer in the solution environment, the molecule was relaxed without any constraints.

All energies were normalised to the lowest energy molecular conformer to calculate the relative energy differences between the conformers.

2.3 Bulk Intrinsic Synthon analysis

The bulk intrinsic synthon analysis was carried out using the HABIT98 software developed at the University of Leeds.[73] HABIT98 takes in structural information from existing crystallographic data to construct a series of unit cells in three dimensions, and calculates the pairwise intermolecular interaction between a molecule in the origin unit cell and all the other molecules within a fixed radius from the central molecule.[35,36] In all three structures, the quercetin molecule of the first asymmetric unit of the unit cell was taken as the centre molecule and all intermolecular

interaction were calculated within a sphere of 30Å radius. The calculation of intermolecular interaction energies was performed using the Momany force-field, which contains a Lennard-Jones potential for the VdW interactions, a specific 10-12 H-bonding potential and a Coulombic term with respect to the electrostatic interactions.[74] The contributions per functional group and per atom type to the total lattice energy of each structure were calculated using the DEBUG-2 function, and were summed over the asymmetric unit. The ranking of the intermolecular interactions by strength was outputted using the DEBUG-1 function. All visualization of molecular and crystal packing were carried out in Mercury CSD 3.10.[75]

The unit cell density was calculated using Equation 1:

$$Unit\ cell\ density = \frac{Molecular\ formula\ weight \times Z}{Unit\ cell\ volume} \quad (1)$$

where Z is the number of asymmetric units in the unit cell.

The sequence of calculations followed for the conformational and bulk intrinsic synthon analysis are illustrated in **Figure 2**.

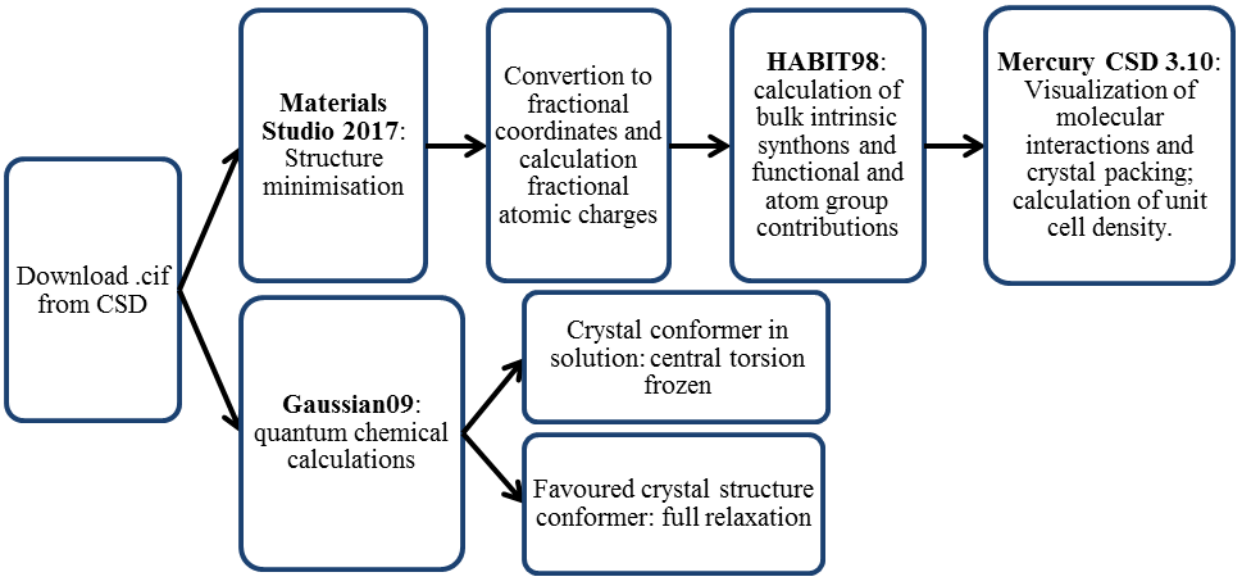
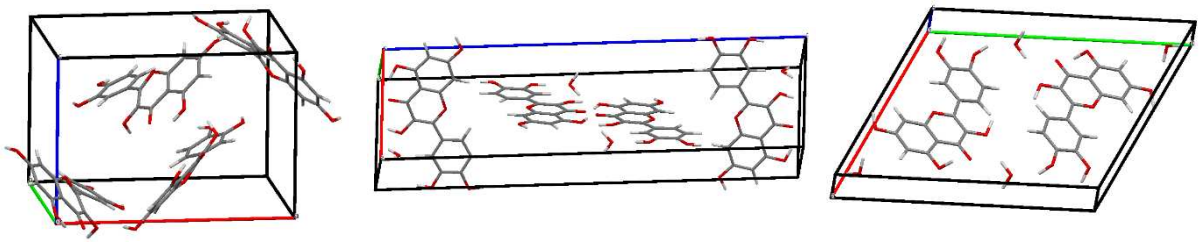


Figure 2: Flow diagram for the structure files preparation and sequence of calculations for the conformational and bulk intrinsic synthon analysis.

3. Results and Discussion

3.1 Unit Cell and Donor/Acceptor ratio Analysis

The unit cell packing and crystallographic data for quercetin anhydrous, monohydrate and dihydrate, as obtained from the Materials Studio optimised files, are illustrated in **Figure 3** and **Table 1**. In the table Z is defined as the number of asymmetric units while Z' is the number of molecules in each asymmetric unit. QA crystallizes with 4 quercetin molecules, and QMH with 4 quercetin and 4 water molecules, in orthorhombic and monoclinic unit cells respectively. QDH crystallizes with 2 quercetin molecules and 4 water molecules in a triclinic unit cell.



(a) (b) (c)

Figure 3. Unit cells of (a) Quercetin anhydrous (b) Quercetin monohydrate (c) Quercetin dihydrate

The density of the unit cell for each structure was calculated and it was found that the QMH and QDH structures present very similar values, whereas that of the QA structure is significantly lower. It is generally assumed that denser crystal forms are more thermodynamically stable than their less dense counterparts, for the same host molecules.[76]

Table 1. Unit cells parameters of quercetin structures. Z is the number of asymmetric units and Z' the number of molecules in each asymmetric unit.

Name	**Quercetin anhydrous**	**Quercetin monohydrate**	**Quercetin dihydrate**
Formula	C_{15} H_{10} O_7	C_{15} H_{10} O_7 .H_2O	C_{15} H_{10} O_7 .2H_2O
Space Group	$P2_1/a$ Orthorhombic	P $2_1/c$ Monoclinic	P 1 Triclinic
Cell Lengths (Å)	**a** 14.7998 **b** 11.2379 **c** 10.3512	**a** 8.7370 **b** 4.8520 **c** 30.1600	**a** 13.109 **b** 17.026 **c** 3.67
Cell Angles (°)	**α** 90.0000 **β** 90.0000 **γ** 90.0000	**α** 90.0000 **β** 95.5200 **γ** 90.0000	**α** 98.18 **β** 90.342 **γ** 119.638
Cell Volume (Å^3)	1721.6	1272.61	701.931
Cell Density (u/Å^3)	0.702	1.007	0.964

Z, Z'	4, 1	4, 2	2, 3
Donor/acceptor ratio	0.357	0.438	0.500

A donor/acceptor ratio (d/a ratio) analysis was carried out for the quercetin structures, as described by Desiraju.[13] This analysis allows the identification of all the donors and acceptors of the asymmetric unit that could potentially be involved in a hydrogen bond interaction are considered, and not only those that actually form hydrogen bonds.

The d/a ratio is a ratio between all the hydrogen bond donors and acceptors in the asymmetric unit of the considered structure (QA, QMH and QDH) that could potentially be involved in a hydrogen bond interaction. Since the quercetin molecule is made of only C, O and H atoms it contains five potential hydrogen bond donors (the H atoms in the hydroxyl groups) and 14 hydrogen bond acceptors (the lone pairs of electrons on the O atoms of the hydroxyl groups, the carbonyl bond and the keto group), as shown in Figure 4. Table 1 shows that the d/a ratio for the quercetin structures follows the trend QA < QMH < QDH. The inclusion of one water molecule in the lattice introduces two additional donors (hydrogen atoms) and two additional acceptors (two lone pairs of electrons on the oxygen atom) in the asymmetric unit, which reduces the imbalance of donors to acceptors and pushes the d/a ratio towards unity.

QA has a d/a ratio of 0.357, below the characteristic value of 0.5, which has been identified as the threshold below which organic molecules have high tendency to form hydrated crystal structures.[13]

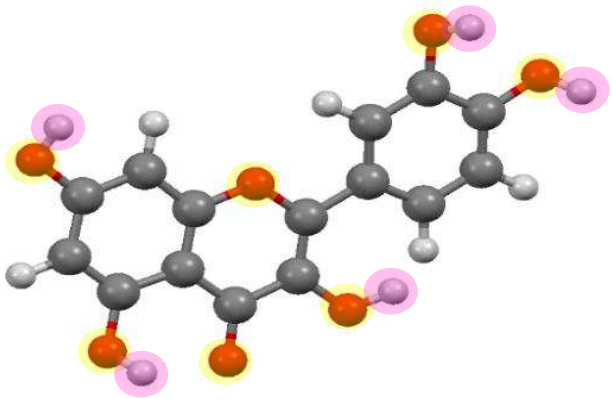


Figure 4. Hydrogen bond donors (highlighted in pink) and hydrogen bond acceptors (highlighted in yellow), for the quercetin molecule. Colour code: Grey- carbon atoms, red-oxygen atoms, white-hydrogen atoms.

3.2 Conformational analysis

The geometry and conformation of the quercetin molecule in the three solid forms has been studied and results were compared. The torsion angle of the phenyl to the pyrone ring of the quercetin molecules in each solid form has been calculated and it is illustrated in **Figure 5**. It is observed that the torsion angle is greatest (31.5°) for the anhydrous structure. This torsion angle leaves the molecule much less planar compared to the monohydrate and dihydrate structures, which present torsion angles of -1.0° and 6.7° respectively.[32]

The energy of the quercetin molecules in their different crystal structure conformations was calculated, to compare the impact that the change in molecular conformation has on molecule stability. It was found that their energy ranking was of the order QDH > QA > QMH. However, upon optimisation of the structures in the aqueous environment, the quercetin molecules both in the QMH and QDH structures optimised to almost the same conformation, which has a torsion angle of close to 17° about the central degree of freedom. In contrast, quercetin in QA optimised

to a more twisted conformation which was calculated to be approximately 2.6 kcal/mol less stable than the conformer found from optimisation of the QMH and QDH crystal structure quercetin molecules.

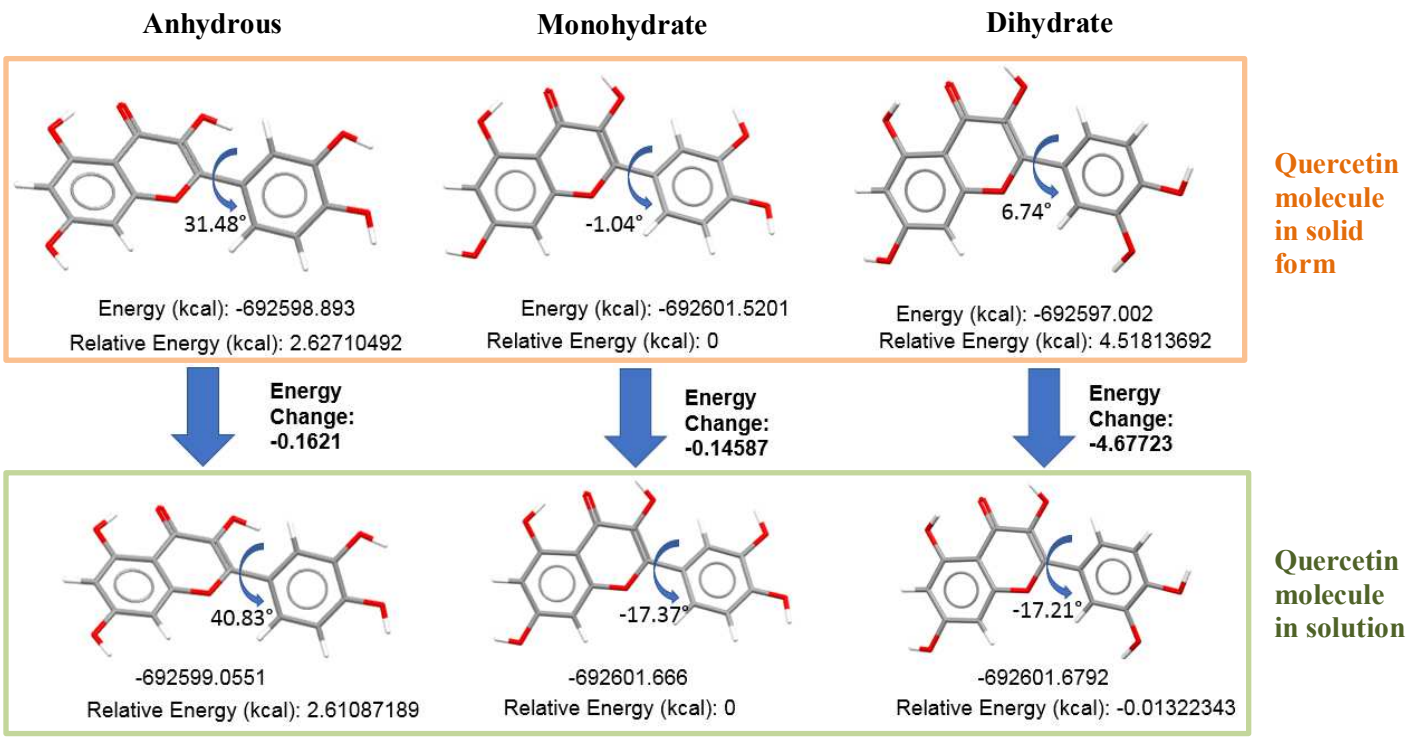


Figure 5. DFT geometry optimisation in an aqueous environment of the anhydrous, monohydrate and dihydrate crystal structure conformers of quercetin. The monohydrate and dihydrate optimise to almost the same twist about the central torsion, whilst the anhydrous optimises to a significantly different conformation.

These results suggest that that QMH quercetin molecular conformation is closest to the most stable conformation in the solution, with it only showing a small energy penalty to go from its optimised conformer to its crystal structure conformer. Despite the QDH molecule doing more

energetic work to go from optimised conformer to crystal structure conformer, it should be observed that it is optimised to the same conformer as the QMH conformer, suggesting there is a low energy pathway between the crystal structure conformer and optimised conformer.

In comparison, the QA conformer optimised to a completely different structure, suggesting that the crystal structure conformation is not close to the most stable solution conformation and instead it optimises to a local stable minimum. Hence, one would assume that if the conformation is fluctuating in the dynamic solution state, it is more likely that the conformation would fluctuate to conformers which are close to its global minimum, such as the local minimum found from the QA geometry optimisation or the QMH and QDH conformers. Therefore, it can be postulated it is less energetically likely for the quercetin molecule to randomly fluctuate into the QA conformation, in favour of the local minimum found from the QA optimisation or the QMH or QDH conformers, suggesting that this would provide an energetic barrier to crystallisation.

Literature solubility studies indicates that the QDH structure is thermodynamically more stable than the QMH form below 100°C.[33] However, the conformational analysis presented here indicates that the QDH needs to do more energetic work to transition into its crystal structure conformation, in comparison to QMH. It is possible that, during nucleation from solution, the smaller amount of de-solvation necessary for the formation of QDH and a more energetically favourable intermolecular packing play a greater role than the conformation, driving the crystallisation of the QDH form over the monohydrate. This is further corroborated by the results of the synthonic analysis shown in the following paragraphs.

3.3 Bulk Intrinsic Synthon Analysis

The main bulk intrinsic intermolecular synthons in the three structures were computed using HABIT98 and ranked by strength using the DEBUG-1 function. The three strongest intermolecular synthons in each structure, those having the highest energy in kcal mol^{-1}, were calculated and are illustrated in Figures 6, 7 and 8 for QA, QMH and QDH respectively. Table 2 summarises the information for these synthons.

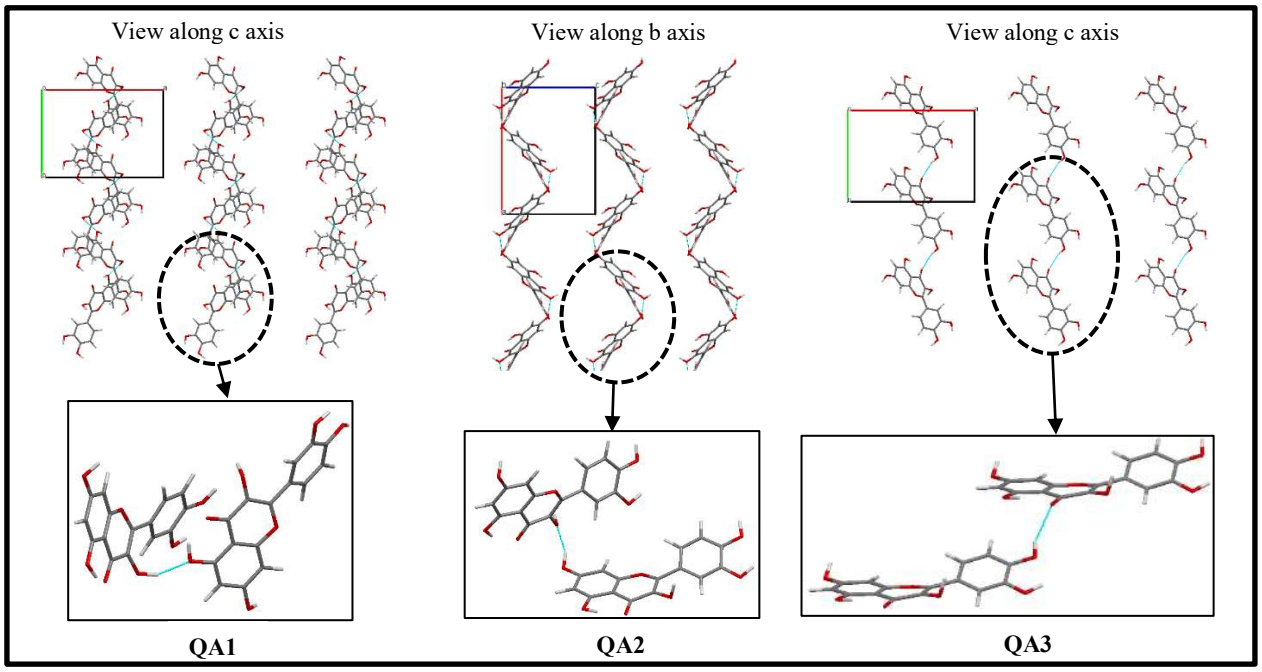


Figure 6. Key intermolecular synthons in quercetin anhydrous ordered by synthon strength. Light blue dotted lines indicate hydrogen bonding

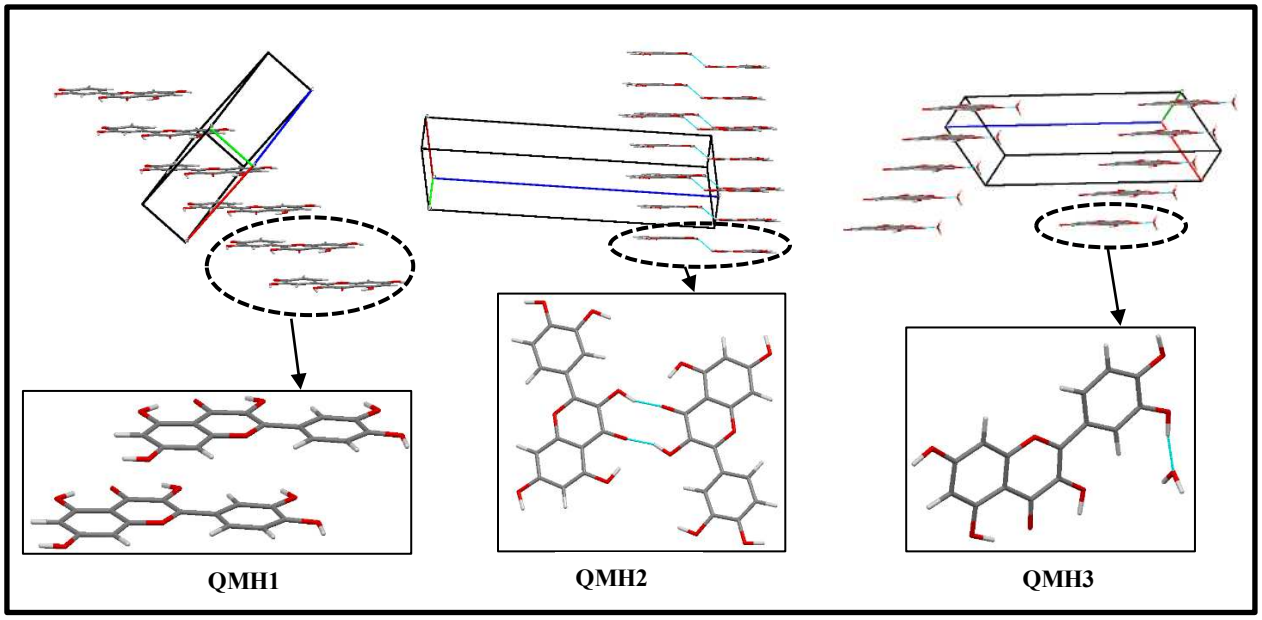


Figure 7. Key intermolecular synthons in quercetin monohydrate ordered by synthon strength. Light blue dotted lines indicate hydrogen bonding

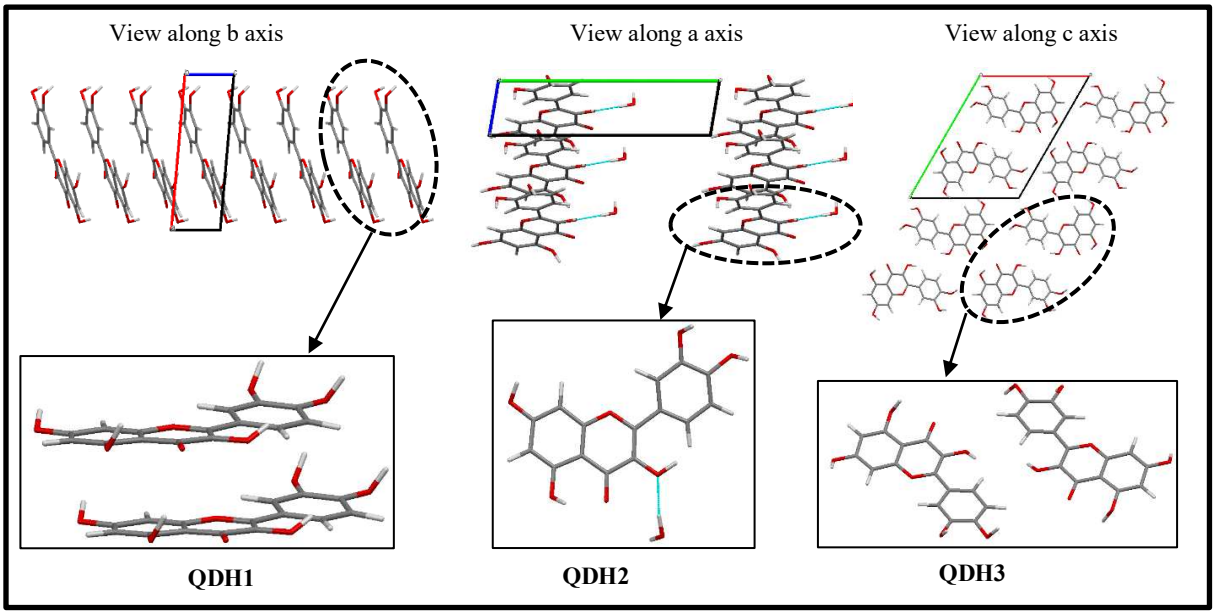


Figure 8. Key intermolecular synthons in quercetin dihydrate ordered by synthon strength. Light blue dotted lines indicate hydrogen bonding

1 **Table 2**. Summary of intermolecular synthons in QA, QMH and QDH structures

Quercetin structure	**Synthon**	**Molecules involved**	**Main synthon type**	**Inter-molecular distance (Å)**	**Synthon energy (Kcal mol^{-1})**	**% contribution to lattice energy**
Anhydrous	QA1	Quercetin - Quercetin	Hydrogen bond	6.93	-4.26	38.4%
	QA2	Quercetin - Quercetin	Hydrogen bond	7.57	-2.86	25.8%
	QA3	Quercetin - Quercetin	Hydrogen bond	11.24	-1.57	14.1%
Monohydrate	QMH1	Quercetin – Quercetin	π-π stacking	4.85	-6.39	24.5%
	QMH2	Quercetin – Quercetin	Hydrogen bond	7.99	-5.33	10.2%
	QMH3	Quercetin - Water	Hydrogen bond	5.93	-2.55	9.8%
Dihydrate	QDH1	Quercetin – Quercetin	π-π stacking	3.67	-7.66	37.8%
	QDH2	Quercetin – Water	Hydrogen bond	5.64	-1.61	7.9%
	QDH3	Quercetin - Quercetin	Permanent dipole-dipole	9.14	-1.43	3.5%

2

In QA, the three strongest interactions in the lattice are found to be mainly hydrogen bonds between quercetin molecules, whereby the QA2 forms an unbroken chain of quercetin molecules running along the a-direction of the lattice.

Table 3 shows that a quercetin molecule is found to form hydrogen bonds with six other quercetin molecules. The carbonyl bond and hydroxyl groups of the quercetin molecule are involved in the hydrogen bonding. The non-planar conformation of the quercetin molecule facilitates close contact between the hydroxyl and carbonyl groups, in order to maximize the number and strength in energy of these interactions. This is demonstrated in Figure 6, where the twisted conformation of quercetin allows for the close contacts between the hydroxyl and carbonyl groups to form the QA3 synthon.

However, the non-planar conformation of the molecule does not allow the formation of strong π-π stacking interactions which can be observed in the two hydrates structures, as shown in Figure 7 and Figure 8. Stacking interactions in the anhydrous form are not found to be among the three strongest interactions in the lattice. This suggests the less closely packed nature of the quercetin molecules in the anhydrous form.

Table 3. Hydrogen bonding interactions in QA, QMH and QDH

Quercetin structure	Number of quercetin-quercetin hydrogen bonds	Number of quercetin-water hydrogen bonds
Anhydrous	6	0
Monohydrate	6	4
Dihydrate	0	6

The strongest intermolecular synthons in the QMH and QDH structures, named QMH1 and QDH1 respectively, are π-π stacking interaction between quercetin molecules. The main contribution to this type of interaction comes from the aromatic carbon atoms of the phenyl and pyrone rings of the quercetin molecules, which interact via Van der Waal forces of attraction. In both hydrated structures, these interactions promote the formation of uninterrupted chains of stacked quercetin molecules packed in an offset orientation, thought to maximise the interaction between the negative central aromatic π-system and the positively charged hydrogens on the outer ring.[77] These strong interactions promote the close packing (shorter intermolecular distances) of the quercetin molecules in the two hydrates.

Comparison of the QDH1 to QMH1 shows that the π-π stacking interaction in the dihydrate form is stronger, with shorter intermolecular distances compared to that of the monohydrate. The π-π stacking interaction in the dihydrate is the dominant synthon, contributing to almost 38% of the total lattice energy. Clearly, the addition of the second water molecule in the unit cell of QDH indirectly influences the interactions among quercetin molecules, allowing them to pack closer together by forming stronger bonds.

In the two hydrated forms, synthons QMH3 and QDH2 are both hydrogen bond interactions between a hydroxyl group of a quercetin molecule and a water molecule. In both cases the interaction creates a channel of water molecules running parallel to the stacked chain of quercetin molecules. Under conditions which promote dehydration of the hydrated structures, the packing of water molecules in the two hydrates is expected to influence the dehydration mechanism.[78,79]

Unlike the anhydrous form, in both hydrates all of the hydroxyl groups of the quercetin molecules are forming at least one hydrogen bond, indicating that water compensates for

unsatisfied hydrogen bonding. As presented in Table 3, in the QMH structure hydrogen bonding is partly satisfied by interactions among quercetin molecules and partly by quercetin-water interactions, whereas in the dihydrate form all hydrogen bonding is satisfied exclusively by interactions between quercetin and water molecules. The contribution of the quercetin and water molecule interaction energies to the total lattice energy of each structure were calculated. As shown in Figure 9, the contribution of water to the total lattice energy increases with the number of water molecules per unit cell, indicating the tendency of incorporation of water molecules into the lattice, and that the formation of interactions between quercetin and water is favoured. The water molecules are found to contribute to 23% of the total lattice energy of QDH, highlighting the significance of the quercetin-water interactions in this structure.

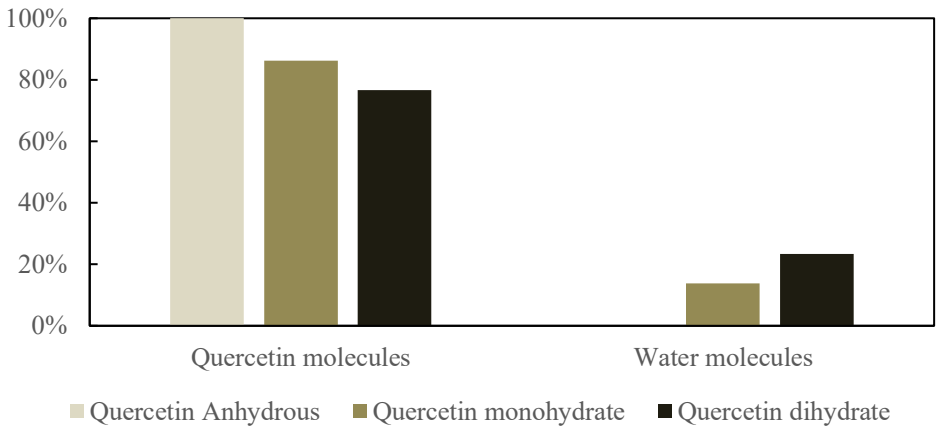


Figure 9. % contributions of quercetin and water molecules' interactions to total lattice energy of the three structures

In conclusion, the results of the present modelling analysis show that, as the degree of hydration and the number of water molecules in the unit cell increases for the three quercetin structures:

(1) hydrogen bonding in the lattice is more satisfied by interaction with the incorporated water molecules, allowing a more planar conformation for the quercetin molecules in the two hydrate structures

(2) the contribution of the π-π stacking interactions between quercetin molecules to the stabilization of the crystal lattice increases.

It is obvious from literature that crystallization of quercetin from an aqueous solvent always produces the dihydrate form.[16,30] This behaviour is explained by the modelling results is as follows:

- During crystallization from an aqueous solvent, the water molecules being much smaller in size compared to quercetin molecules, can be positioned close to the polar groups of the quercetin molecule forming hydrogen bonds;
- Once hydrogen bonding is satisfied, the quercetin molecules, having a more planar configuration, can pack more closely and efficiently via strong π-π stacking interactions;
- The smaller amount of de-solvation and conformational rearrangement in the dihydrate structure probably results in the easier crystallisation of this form from aqueous solution. This agrees with the higher calculated unit cell density which predicts a greatest stability;
- Quercetin in QA must take an energetically unfavourable conformation to satisfy its hydrogen bonding groups, thus ends up having a lower thermodynamic stability, and is not preferentially nucleated from an aqueous solvent.

From the points above, we summarise that the favourable packing of the quercetin-water H-bonding and quercetin-quercetin π-π stacking, rather than the conformational stability, results in the dominant crystallisation of the dihydrate form. We do however believe that the unfavourable conformation of the anhydrous form plays some role in making this structure especially challenging to nucleate.

The modelling results shown here highlight the importance of the water molecules in the stabilization of the crystal structures of QMH and QDH, as they can influence the hydrogen bonding pattern and affect the strength and nature of intermolecular interactions formed. These results agree with experimental studies on the relative stability of quercetin and its hydrated forms. [17,28,31-33]

In conclusion, this works can explain why quercetin preferentially crystallizes as hydrated form from aqueous solvents and why polymorphic transitions from the QA to a hydrate are favourable in environments with high humidity.[17, 33]

4. Conclusions

In this work, synthonic modelling and molecular conformational analysis were used to study three different crystalline structures of quercetin: the anhydrous, monohydrate and dihydrate forms. The role of water molecules within the structures was studied to understand how it affects the packing and conformation energetics of quercetin crystals. By analysing the bulk chemistry of QA, it was found that all key synthons are polar interactions, involving hydrogen bonds and permanent dipole-dipole interactions, while in the QMH and QDH structures the synthon contributing more to the lattice energy is a non-polar π-π stacking interaction. The hydrogen bonding interactions in the two hydrates are satisfied partly (QMH) or exclusively (QDH) by interaction with the water molecules.

The results of the synthonic modelling can explain the crystallization behaviour of quercetin reported in literature and its tendency to crystallize or transform in the dihydrated form in the presence of water molecules. A conformational analysis was also performed and revealed that the quercetin molecules within QA are organized in a less planar arrangement, thus being unable to

pack as efficiently as in the hydrated crystals and resulting in a lower unit cell density. The quercetin molecules in the QMD and QDH are arranged in a more planar way, since quercetin hydrogen bonding is satisfied by the presence of water molecules.

In conclusion, this work shows how synthonic modelling and conformational analysis can be used as a predicting tool to better understand the relationship between crystal structure and product properties (particularly stability), leading to a more efficient product formulation and faster development, but also as a tool to predict and design crystallization processes in order to obtain crystals with desired physiochemical properties.

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Supporting information

Supporting information show the applicability of the Dreiding forcefield for the system in study. Changes in unit cell lengths and angles resulting after optimization of quercetin anhydrous, quercetin monohydrate and dehydrate using the Dreiding forcefield are presented.

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For Table of Contents Use Only:

Synthonic modelling of quercetin and its hydrates: explaining crystallization behaviour in terms of molecular conformation and crystal packing

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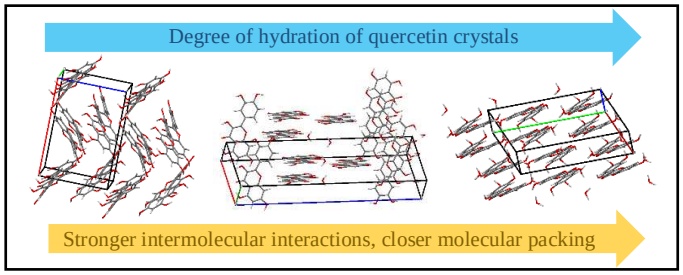

Synopsis:

The crystal structure, packing and conformation energetics of quercetin anhydrous, monohydrate and dihydrate are studied here using synthonic modelling. Calculations show that incorporated water can satisfy the hydrogen bonding interactions within quercetin molecules allowing them to adopt a more planar conformation and enabling strong π-π stacking interactions. As a result, hydrated forms show more close-packed and stable structures than the anhydrous.