

Oiling out or molten hydrate – liquid-liquid phase separation in the system vanillin-water

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ABSTRACT

Vanillin crystals in a saturated aqueous solution disappear and a second liquid phase emerges when the temperature is raised above 51°C. The phenomenon has been investigated with crystallization and equilibration experiments, using DSC, TGA, XRD and hot-stage microscopy for analysis. The new liquid solidifies on cooling, appears to melt at 51°C, and has a composition corresponding to a dihydrate. However, no solid hydrate can be detected by XRD, and it is shown that the true explanation is that a liquid-liquid phase separation occurs above 51°C where the vanillin-rich phase has a composition close to a dihydrate. To our knowledge, liquid-liquid phase separation has not previously been reported for the system vanillin-water, even though thousands of tonnes of vanillin are produced globally every year.

Keywords: oiling out; polymorphism; pseudopolymorphism; hydrates/solvates; solubility; thermodynamics; solid state stability; phase separation; phase diagram

INTRODUCTION

The thermodynamics and kinetics of organic substances can be quite complex, as witnessed by the frequent occurrence of polymorphs and solvates. In a survey from 1997 it is reported that more than half of the active pharmaceutical ingredients in use can crystallize in more than one polymorphic form¹. Regarding pseudo-polymorphism, in 1980 it was estimated that approximately one third of all pharmaceutical ingredients were reported to have the capability to form crystalline hydrates², while 57% of the pharmaceuticals in the 1991 European Pharmacopoeia have reported hydrate forms³. If other solvents are considered, these numbers rise further. This multiplicity of paths available to the molecules in crystallization can lead to problems, as different polymorphs and solvates of a substance differ in their physical properties, such as rate of dissolution (affecting bioavailability), stability, toxicity, and formulation parameters such as powder flow, compactibility, lubricity and hardness^{4,5}. Besides using different temperatures and cooling rates, manufacturing processes often involve different solvents; hence, understanding the thermodynamics and kinetics of crystallization for the particular system is of great importance. Furthermore, processes like drying, mixing and storage subject the drug substances to varying pressures, temperatures, shear stresses and

humidities, which can trigger unwanted polymorph transformation, solvation or desolvation. For these reasons, the characterization of the occurrence of polymorphs as well as solvates is part of the mandatory study of prospective drug substances⁶.

In the work reported here, vanillin was one of the model substances included in a polymorph screening study. In the work on vanillin in water we found a region of “oiling out”. In the present paper we describe the process of finding the true explanation for, and the properties of, this phenomenon. This paper also serves as an illustration of how complex and fascinating the exploration of polymorphism can be. In our case, early during the work we considered only the simple explanations and formed conclusions which later were difficult to abandon even though question marks were gradually piling up. Hence, this paper also illustrates the importance of keeping an open mind, especially when performing a polymorph screening. Chemistry is the science of atoms and molecules, but normally we do not directly observe what happens at the molecular level. We rely on observations of which we are capable, and use theory and experience to infer explanations of the underlying chemistry. As a result, exploration of crystallization properties can sometimes turn into a kind of detective work, where mistakes can be made, leading to the wrong conclusions. In the present work, a second viscous liquid appearing in the system was assumed to be the molten state of an as yet unknown hydrate. As such we were prepared to propose an alternative mechanism behind what is usually called oiling out. However, further studies revealed that a liquid-liquid phase split interfered with the solid-liquid equilibrium, where one of the liquid phases had a composition close to a dihydrate.

Vanillin [121-33-5] or 4-hydroxy-3-methoxybenzaldehyde is a commercially important substance with a wide range of uses, most importantly as an aroma chemical used as a flavouring agent in the food industry⁷. In smaller quantities, it is used as a fragrance chemical in perfumes, as an intermediate in the pharmaceutical industry, and as a reagent in analytical chemistry. It is also patented as an anti-UV agent. Less than one percent of the total, global production of vanillin, which amounts to about 12,000 tonnes annually, is in the form of vanilla extract⁸. Synthetic vanillin has been produced industrially since 1894, and is today obtained either by processing waste sulphite liquors containing lignin, or by synthesis from guaiacol. Vanillin is a weak acid, and a moderate hydrogen bond acceptor. The molecule possesses the three highly reactive methoxyl, phenol and aldehyde groups. Vanillin can undergo a number of reactions, including a slow oxidation into vanillic acid on contact with air⁷.

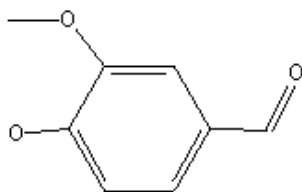


Figure 1. The vanillin molecule.

Cartwright⁹ reports the solubility of vanillin in water up to 50°C, which, together with contributions from other sources^{10,11} is presented in fig. 2.

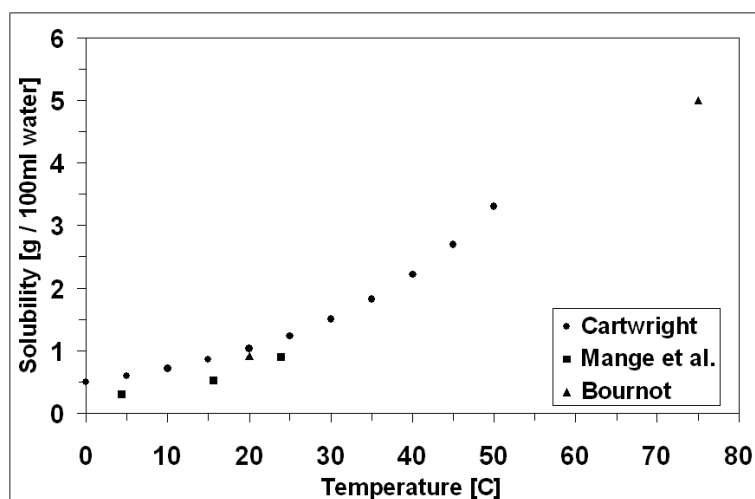


Figure 2. Solubility of vanillin in water as reported in the literature.

The polymorphic situation of vanillin is not satisfactorily settled. Several observations have been published, starting with Gaubert¹² who as early as 1922 reported four polymorphs. McCrone, using only a microscope, also found four forms¹³, whereas Hussain reports two¹⁴. The findings contradict each other, however, and neither author reports melting points. There is only one reported case of liquid-liquid phase separation involving vanillin, and this is in a solvent mixture of 20 mass-% of 2-propanol in water¹⁵.

EXPERIMENTAL WORK

Materials and equipment

Vanillin (≥ 99.9 mass-% of USP, BP and Eur.Ph. Grade) was supplied by Borregaard Synthesis (Norway) and was used as received.

For differential scanning calorimetry (DSC), a TA instruments DSC 2920 with hermetically sealed aluminium pans, calibrated according to standard procedure against the melting point of indium, was used. For hot-stage microscopy (HSM), a set-up consisting of a Mettler FP 82 hot-stage, a Mettler FP 80 central processor, and a Hitachi HV-C20 camera connected to an Olympus BH-2 light microscope was used. Thermal gravimetry (TGA) was carried out using a Perkin Elmer TGA7 flushed with dry nitrogen gas. For powder diffraction X-ray analysis, a Siemens D55 powder diffractometer, with $\text{CuK}\alpha$ -radiation, was used. Single-crystal XRD was performed with a Bruker-Nonius KappaCCD diffractometer.

Experiments at elevated temperatures were conducted by immersing sealed 200 ml flasks equipped with magnetic stirrers, or racks of test tubes, containing solutions into a Julabo FP45 programmable, thermostatic water bath. Cooling crystallization was performed in a 1 L stirred, jacketed batch crystalliser connected to said bath.

Procedures and results

Thermal characterization of vanillin

Two techniques were used to determine the melting point of pure vanillin crystals; differential scanning calorimetry (DSC) and hot-stage microscopy (HSM). The reported melting points obtained by DSC are the extrapolated onset temperatures, since these temperatures generally show less variance than the peak temperatures¹⁶. The onset temperatures are defined as the temperatures where the baseline intersects the extrapolated tangent at the midpoints of the

peaks, and were calculated using the TA Instruments Universal Analysis software. In DSC, samples were analysed at heating rates of 1°C/min, 5°C/min and 10°C/min, with five runs per setting. At 1°C/min, samples of pure vanillin melted at an extrapolated onset temperature of 80.0 °C (with a standard deviation of ± 0.2 °C), peaking at 80.9(± 0.3) °C, and with a melting enthalpy of 144.9(± 5.5) kJ/kg. At 5°C/min, the extrapolated onset temperature was 80.0(± 0.1) °C, the peak temperature 81.8(± 0.3) °C and the melting enthalpy 143.3(± 3.0) kJ/kg. At 10°C/min, the extrapolated onset temperature was 79.3(± 0.1) °C, the peak temperature 81.4(± 0.2) °C and the melting enthalpy 150.3(± 8.2) kJ/kg. In HSM, at a heating rate of 5°C/min, the crystals were seen to melt between 80°C and 82°C.

Molten hydrate – oiling out experiments

Crystallization experiments were originally performed on vanillin as part of a polymorph screening. At high temperatures, a viscous liquid phase was found to separate from the aqueous solution. This led our interest into the phenomenon known as oiling out, sometimes causing significant problems in the industry, but of which little is reported in the literature. A number of experiments were carried out in order to investigate this. Here, we give a chronological account of seven of these experiments. Experiment no. 1 was a thermal characterization of crystals from an aqueous solution. Experiments no:s 2 – 3 were designed to explore the properties of the second liquid phase, while in experiment no. 4, the temperature dependence of the emergence of the second liquid phase in solutions of different concentrations was investigated. In experiment no. 5, thermogravimetric analysis was used to determine the water content of the material obtained upon solidification of the new liquid at room temperature. Finally, in experiments no:s 6 – 7, X-ray diffraction analyses were employed to identify the structure of this solid material.

In experiment no. 1, crystals of vanillin were produced by cooling crystallization. A saturated aqueous solution of vanillin at 50°C (~3.3 g/100 ml water; cf. fig. 2) was prepared by mixing an excess of solid vanillin with water. The mixture was stirred for one hour at 50°C. Then 150 ml of the saturated solution was filtered into the crystalliser kept at 60°C. After 30 minutes at 60°C the temperature was ramped from 60°C to 20°C at 1°C/min. At a bath temperature of 21°C a very rapid nucleation could be observed. The resulting crystals were filtered and spread out to dry at room temperature for approximately one hour. The crystals were light, white needles, of about a millimetre in length. The crystals were analysed by DSC (5°C/min) one hour after filtration, after 24 hours of drying spread out in darkness at room temperature, and again after ten days of further drying, and the thermograms are shown in fig. 3.

Initially, the sample yielded one major, sharp endotherm with an onset temperature of 52°C. Furthermore, there was some slight endothermic activity at 70-80°C, followed by major endothermic activity from around 90°C to past 100°C. 24 h later the sample showed a small endotherm at 52°C, and a large one with an onset temperature of between 70-76°C. The final thermogram, after ten days of drying, shows a faint trace of endothermic activity at 51°C and a big, well-defined endotherm with an onset at 80.2°C.

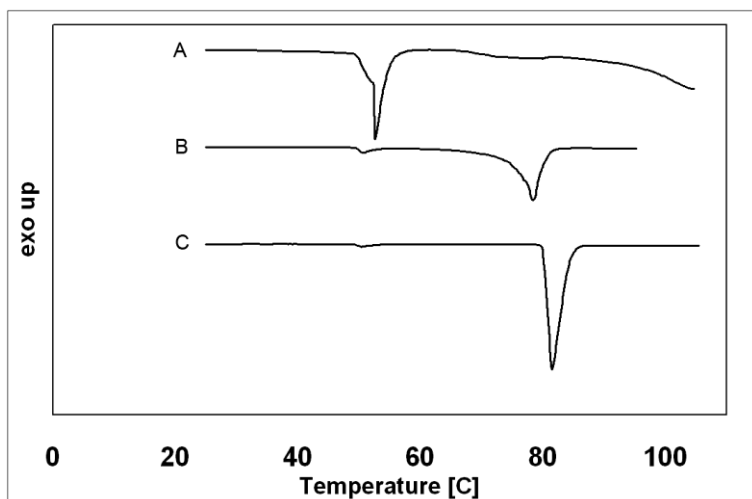


Figure 3. DSC thermograms of vanillin crystallized from water. A = directly, B = after 24 h, C = after ten days.

In HSM at 5°C/min, samples were first analysed with the crystals uncovered on the slide, and then using a coating drop of Si-oil to detect¹⁷ or prevent the evaporation of possible hydrate water. With the crystals uncovered, there were no visible changes occurring until around 80°C, when the crystals melted. When samples were covered with a drop of oil, the crystals were seen to melt at temperatures between 51°C and 63°C.

In experiment no. 2, 100 ml of distilled water was mixed with 12 g vanillin in a flask. The amount of vanillin is well in excess of the reported solubility at all working temperatures (cf. fig. 2 – the solubility ranges from ~1 g/100 ml water at 20°C to ~5 g/100 ml water at 80°C). The flask was allowed to equilibrate for 24 h at 55°C. By then the solution contained no visible crystals, but two separate, distinct liquid phases. The topmost phase had a volume perhaps ten times that of the lower liquid. The flask was allowed to remain at 55°C for several days, occasionally agitated by swirling or with the magnetic stirrer. In spite of this treatment, no crystallization was observed in the flask at or above 55°C. A sample of the bottom liquid phase was extracted, using a pre-warmed Pasteur pipette, and was placed in a glass vial at room temperature. The liquid was found to be yellow, transparent, and viscous. The yellow colour was initially pale, but darkened with time. When the sample was moved to room temperature, crystallization occurred immediately, resulting in a yellowish, agglomerated solid mass with essentially no observable free liquid. In DSC analyses carried out immediately, the material was found to melt at an onset temperature of 51°C.

In experiment no. 3, 12 g vanillin was dissolved in 100 ml distilled water by heating to 55°C, at which time the second liquid phase supplanted the solids. The topmost phase was decanted off, and a small test tube was filled to one half with the dense liquid using a pre-heated Pasteur pipette, and was put through a series of cooling-heating cycles. The tube was tightly sealed, and was initially kept still at room temperature whereupon the liquid started to crystallize directly. Crystallization originated independently at several points in the liquid body, and was complete after approximately ten minutes. When crystallization had taken place, the tube was moved to the 55°C-bath, at which the sample immediately started to melt again. Eventually the entire sample melted, resulting in a yellowish, viscous liquid. The crystallization-melting sequence was repeated for the same sample, with identical results.

In experiment no. 4, 12 g of solid vanillin was added to 50 ml and to 75 ml distilled water respectively, and the mixtures were placed in a 40°C bath and agitated with magnetic stirrers.

The temperature was then raised gradually, first to 45°C, then in increments of around 1°C, with at least six hours between each step. Before every increase in temperature, the stirring was temporarily halted and the contents of the flasks allowed to settle, followed by observation and registration of the exact bath temperature. Excess solid crystalline material was present in both flasks right until the moment of transformation into a second liquid, which occurred for both solutions between 50.0°C and 51.3°C. The transformation was sudden, and complete, i.e. at the transformation temperature there was a clear transformation from solid crystals present in a single-phase liquid into a two-phase liquid-liquid system with no solids present. At temperatures above 51.3°C the flasks contained no crystals, only the clear, topmost phase, and a denser, yellow phase.

In experiment no. 5, a liquid-liquid mixture was created as in experiment no. 2 and allowed to equilibrate for 24 hours. After allowing the phases to separate for 30 min at 55°C without stirring or swirling, the topmost phase was removed completely, by means of decantation and a pre-heated Pasteur pipette. A sample of about 19 mg of the dense liquid phase was then extracted by a pre-heated Pasteur pipette, and put in a platinum TGA sample pan, whereupon it was allowed to crystallize. The sample was then immediately analysed at a heating rate of 5°C/min, and the result is presented in fig. 4. The TGA curve shows that evaporation begins directly, and accelerates until approximately 60°C, from which point the mass is quite constant up to about 75°C, where a second drop in mass follows, the onset of which is sharper, and the range narrower compared to the first period of weight loss. The total reduction in mass from start to finish amounts to 19.3 per cent, split into a 13.2 per cent loss during the first stage and a 6.1 per cent loss during the second. Assuming that all water evaporated from the sample, and that the sublimation of vanillin was negligible in comparison, the molar ratio of water to vanillin can be calculated to 2.0 water molecules per vanillin molecule, using 152.15 g/mol as the molar mass of vanillin¹⁸.

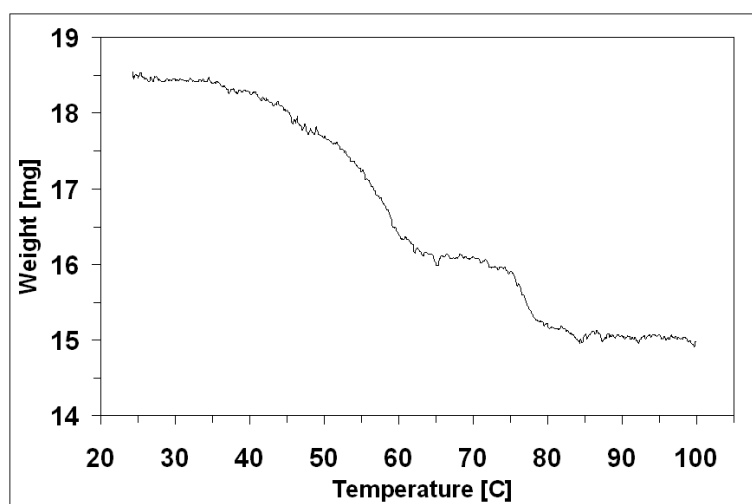


Figure 4. Thermogravimetric analysis of the solidified, dense liquid phase.

In experiment no. 6, crystals were produced by crash-cooling an aqueous solution saturated at 50°C, by moving it from a bath at 68°C to another bath at 1°C. The resulting crystals were small, fluffy needles, sufficiently fine not to require any preparatory grinding. The crystals were analysed immediately with DSC and X-ray powder diffraction. The former showed an endotherm at about 50°C, whereas the powder XRD spectrum proved to be identical to a spectrum of commercially available vanillin, form I. In experiment no. 7, a vanillin-water slurry with 12 g vanillin in 100 ml water was created as before, and heated to 55°C until the second liquid phase had supplanted the solids. Stirring was then halted, and the sealed flask

was placed in room temperature, whereupon the dense liquid phase visibly solidified into a microcrystalline cake. The solution was left for several days, after which time several large, clear crystal plates had emerged. By single-crystal XRD analysis the structure was found to be identical to the one of vanillin form I found in the literature.

The solid-liquid-liquid phase diagram

While it was our original hypothesis that the denser vanillin-rich liquid phase was actually a molten hydrate of vanillin, eventually we came to realise that the situation was rather one involving a liquid-liquid phase separation replacing the solid-liquid equilibrium at about 51 °C. In a separate experimental programme, the liquid-liquid phase boundary was examined. The strategy was to sample points in a flexible grid, using knowledge of similar phase diagrams¹⁹ to select the sample concentrations for each chosen temperature. Two slightly different setups were used, depending on the composition to be sampled. In the water-rich region of the diagram, close to the border between the single liquid phase and the two-phase liquid-liquid zone, solutions were prepared in racks of sealed test tubes with 10 ml of distilled water, each tube with a slightly higher concentration of vanillin than the previous. The tubes were immersed in the water bath, shaken by hand and monitored during several hours. For each tube, one data point for the phase diagram was obtained, labelled L_1 for single liquid or L_1+L_2 for liquid-liquid phase splitting.

For compositions above 20 mass-% of vanillin, a different approach had to be used, because of the large amounts of vanillin having to be dissolved. Sealed Erlenmeyer flasks equipped with magnetic stirrers, each with 10 ml of distilled water, were used, and vanillin was added in amounts ranging from 5 to 10 g, until no more solids could be dissolved. Data points were thus created, and labelled either two-phase (L_1+L_2), single-phase liquid (L_2), or liquid-solid (L_2+S).

The composite phase diagram, resulting from the equilibrium grid sample experiments reported in table 1, and augmented with the literature solid-liquid solubility data, is presented in fig. 5. All compositions are given in mole-% of vanillin on a total basis. Since the solubility of vanillin in water below 51 °C and the composition of the water-rich liquid phase above 51 °C are below one mole-% of vanillin, a logarithmic scale is used for the composition axis, in order to improve readability. The principal location of the zone boundaries are highlighted by solid and dotted lines.

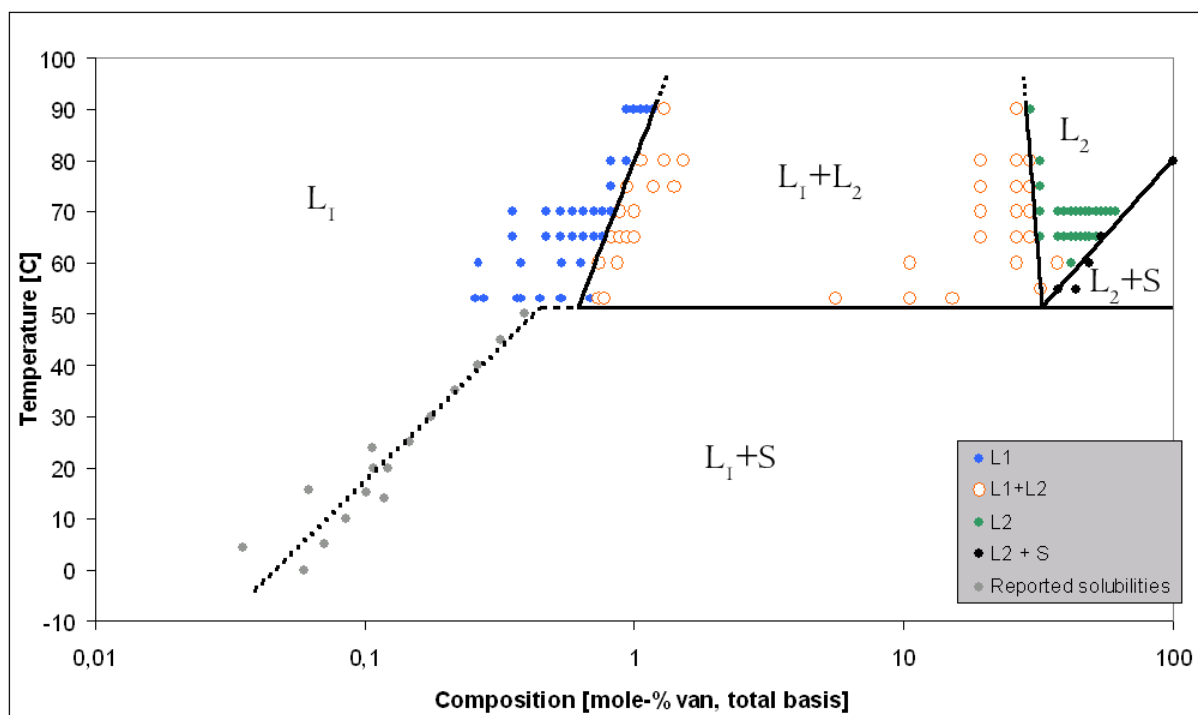


Figure 5. The phase diagram for the two-component system vanillin-water.

Table 1. The experimentally determined locations of the zone boundaries given as composition ranges.

Temperature (°C)	Transition composition range (mole-% van, total basis)		
	$[L_1] \leftrightarrow [L_1+L_2]$	$[L_1+L_2] \leftrightarrow [L_2]$	$[L_2] \leftrightarrow [L_2+S]$
53	0.69 – 0.74	$>32.2^i$	$<37.2^i$
60	0.63 – 0.74	37.2 – 41.6	41.6 – 48.7
65	0.76 – 0.82	29.3 – 32.2	51.6 – 54.3
70	0.82 – 0.88	29.3 – 32.2	$>60.7^{ii}$
75	0.82 – 0.94	29.3 – 32.2	$>32.2^{ii}$
80	0.94 – 1.06	29.3 – 32.2	$\sim 100^{iii}$
90	1.17 – 1.29	26.2 – 29.3	–

ⁱ No L_2 -zone was encountered; the values represent the highest/lowest observed compositions within the respective zones.

ⁱⁱ No L_2+S -zone was encountered; the values represent the highest sampled composition in the L_2 -zone.

ⁱⁱⁱ This value has not been measured, but should theoretically be close to 100% as the melting point of vanillin is almost 80°C.

The short, horizontal dotted line bridging the solid-liquid solubility data points from the literature and our liquid-liquid two-phase zone boundary data in the water-rich region is only a construction. It does not represent the thermodynamics of the system, it only illustrates that there is uncertainty in the determination of the liquid-liquid phase separation. Please note the logarithmic concentration axis and that the concentrations are quite low in this part of the diagram. There are also some inconsistencies in the data points along the boundary between the L_1+L_2 two-phase zone and the L_2 single-phase. This is believed to be due mainly to the difficulty in obtaining complete phase separation because of the high viscosity of L_2 . Furthermore, a thin emulsion at the interface between the liquid phases after suspended stirring or shaking sometimes made observations slightly more uncertain. Another problem was caused by the time it took to reach equilibrium, which was considerable for the experiments carried out at relatively low (50-60°C) temperatures. Consequently, there is a

relatively high degree of uncertainty in the data points at these temperatures. Furthermore, data sampled around the $L_2 / L_2 + S$ border may be slightly unreliable, since at these temperatures, vanillin regularly condenses on cool surfaces such as the underside of the lid and around the edges, depositing some solid material which may interfere with observations of the solution.

DISCUSSION

At first, the results of the crystallization experiments seemed unequivocally to point to the existence of a hydrate. The denser liquid phase was thought to be the molten hydrate, since a sample of the “hydrate” was seen to repeatedly melt and re-solidify at the same temperature in a sealed tube, and since the TGA drying curve showed that the composition of the dense liquid exactly corresponds to that of a dihydrate. Furthermore, faced with the fact that the second liquid phase appeared at the same temperature in slurries of varying composition, and that this conversion was total, one could easily be inclined to believe that in contact with water, vanillin forms a hydrate, with a melting point of 51°C. Finally, how could the fact that crystals produced by controlled cooling, filtered and dried for one hour still melted some thirty degrees below the normal melting point for vanillin otherwise be explained? Sharp, well-defined endotherms in DSC clearly indicated a melting, as did visual observations in the hot-stage microscope when viscous oil was used to prevent gradual evaporation of water from the crystals.

There are several kinds of hydrates, with respect to the manner in which the water molecules are bound to the crystal matrix. One important distinction is between isolated site hydrates and channel hydrates²⁰. In the former, the water molecules are isolated from each other by the matrix of host molecules. The water molecules are involved in well-defined interactions, and the energy required for liberation will be approximately the same for all water molecules. Such hydrates are expected to be stable until the onset of dehydration, then to dehydrate rapidly with one or a few sharp, well-defined peaks in DSC, and a narrow interval of weight loss in TGA. In a channel hydrate, the water molecules are hydrogen bound to other water molecules along an axis or a plane in the crystal matrix. As a result, the liberation of one water molecule exposes others to the surrounding atmosphere. Furthermore, by a mechanism known as inverse sigma cooperativity, the breaking of some bonds weakens the remaining hydrogen bonds, increasing the probability that more water molecules can be liberated. This leads to a continuous dehydration, with a low onset temperature²⁰. In many ways, “wet” vanillin behaves like a channel hydrate, and therefore, the hypothesis was initially that vanillin formed such a hydrate. The gradual evaporation of water starting directly on contact with air and increasing with temperature, as seen in the TGA graph, supported this hypothesis.

The thermodynamic stability of true polymorphs does not depend on the solvent, but of course the situation is different for solvates³. Hence, in a water solution the hydrate could be more stable than the anhydrate, but when exposed to the atmospheric environment it might rapidly lose the hydrate water. This was adopted as the explanation for why crystals of vanillin that had recently been in contact with water would “melt” at 51°C, while crystals that had been kept out of solution at room temperature and normal humidity dehydrated and after a while behaved thermally as pure vanillin. The DSC endotherm at 76°C for crystals that initially melted at 51°C was somewhat speculatively explained by the transformation into a so-called dehydrated hydrate; a crystalline structure that retains the hollows earlier occupied by water molecules, which is less ordered and has lower density than other crystalline forms²¹, although in that case the melting point would be somewhat high. The fact that powder XRD as well as single-crystal XRD showed no sign of a structure different from that of normal

vanillin form I was explained as being due to a very rapid dehydration when the material was exposed to normal atmospheric conditions. From work on hydrates and solvates it is known to sometimes be the case for a phase stable in solution to be so unstable when brought out of the solution that it is very hard to determine its structure. However, this should be more likely to occur for solvates of low-boiling organic solvents like acetone than for hydrates because of the moisture content in the surrounding air as well as the rather high boiling point of water. At the end of the day, however, the hypothesis of a hydrate was re-validated and the situation was examined from the point of view of liquid-liquid separation.

The phase diagram is of the type designated 2-Ia₂ by Nývlt¹⁹. As can be seen in fig. 5, there is a two-phase liquid-liquid zone above 51°C, inside which two conjugated liquid phases are in equilibrium, one of which is water-rich and the other one vanillin-rich. The relative amounts of these phases depend on the overall composition of the system, and the compositions of the two phases depend on the temperature. As was shown by the TGA analysis and corroborated by the phase diagram, the vanillin-rich liquid phase at 51°C contains 81 mass-% of vanillin. If the temperature of this liquid phase is reduced, the material turns into a solid mass, which in the physical reality of the lab is easily perceived as a single solid phase perhaps just slightly moist. We now know, however, that the vanillin actually solidifies without incorporating water molecules into the lattice, but the relative amount of free water is so low that its importance is easily overlooked. The phase diagram is valid whenever there is a two-component system of vanillin and water, and therefore also for wet vanillin crystals. Therefore, as the temperature is increased above 51°C, the material reverts to the liquid state. Even if a considerable amount of water evaporates, as it has for crystals produced from an aqueous solution, which has been insufficiently dried, the phase diagram shows that the L₂ + S border is crossed at temperatures far below the normal melting point of vanillin. Altogether, this easily creates the illusion that the solid phase melts when the temperature rises above 51°C. Out of solution, in air at room temperature and normal humidity, water evaporates from the moist crystals, and the two-component system vanillin-water becomes the single-component system vanillin. This transition will be gradual, and the apparent melting point as observed in DSC will increase as the crystals get drier from 51°C into 80°C for completely dry crystals. This is believed to be the reason for the melting point of 76°C which was observed in experiment no. 1.

The HSM observations are equally easily explained with the phase diagram; without the oil coating, water mixed with the crystals can evaporate as the temperature is increased, and at 51°C, the onset of the transition into liquid for a mixture of the starting composition, only vanillin remains, melting at its normal melting temperature. If, however, water is prevented from evaporating by the drop of oil, the two-component system is intact, and the transition into a liquid L₂ takes place at 51°C, effectively causing the crystals to “melt”.

The phenomenon of oiling out, or the emergence of a second liquid phase during an attempted crystallization, is not sufficiently mapped in the open literature, but it is clear from what is known about it that there are similarities to what has been put forward in this work. Bonnett et al.²² refer to the so-called oil phase as a highly energetic, metastable state – the most unstable state available – that would precede crystallization, in accordance with Ostwald’s rule of stages. They present an example of a substance which, in a particular solvent mixture, forms a so-called oil phase on cooling, which eventually crystallizes, even when held at constant temperature. A discrepancy between this account and our results is to be found in the fact that the oil phase of Bonnett et al. eventually crystallized, even though the temperature remained constant. The second liquid phase of vanillin does not crystallize in solution above 51°C.

Common knowledge among chemists, as well as basic course literature, such as the book by Harwood et al.²³, assign the blame for oiling out to the presence of impurities, or to overly rapid cooling. Harwood et al. also mention the fact that if the temperature of the solution is above the melting point of the pure substance as it comes out of solution, it will appear as an “oil.” In the case of vanillin, however, the melting point of the pure substance is well above the “oiling out temperature”, and the purity of the starting material used in this work is ≥ 99.9 mass-%, although it has to be recognised that vanillin is unstable when exposed to light and oxygen, which was experienced during the experiments as a gradual yellowing of solutions on a time scale of several days.

At temperatures below 51°C, the solubility of vanillin in water is approximately 0.5 mole-% or lower even though the solid state activity is 0.5 if the heat capacity terms are neglected²⁴. Hence, the activity coefficient of vanillin in the solution is in the order of 100; a strong positive deviation from Raoult’s law, describing in a relative sense that vanillin does not associate strongly with water. At temperatures above 51°C, the solubility is quite high starting from 33 mole-% of vanillin at 51°C and approaching unity at increasing temperature. In this temperature region, the mole fraction solubility is quite close to the activity of the solid phase which means that the solution from the point of view of vanillin is close to ideal. Close to 51°C, there is a dramatic discontinuity in the solubility curve – above this temperature, there are two ways that vanillin and water can organise their molecules in solution. At 51°C, the chemical potential of vanillin in the two different liquid environments exactly equals that of the solid phase. Below 51°C, there is only a quite diluted solution where the chemical potential equals that of the solid, while above 51°C, there is only a very concentrated solution in which this criterion is fulfilled. At 51°C and at an overall solution composition of 33 mole-% of vanillin, three phases are at equilibrium, the pure solid and two immiscible solutions, and if the pressure is fixed there are no degrees of freedom.

CONCLUSIONS

Vanillin and water form a system where at temperatures above 51°C and within a certain composition range two liquid phases are in equilibrium. The boundaries of this two-phase region have been determined. This liquid-liquid phase splitting extends above the melting temperature of pure vanillin, form I. The solubility of solid vanillin, form I, in water is discontinuous at 51°C, being no higher than 1 mole-% on a total basis below this temperature, and at least 33 mole-% on a total basis above.

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