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Determination of the solubilities of crystalline solids in solvent media that induce phase changes: Solubilities of 1,2-dialkyl-3-hydroxy-4-pyridones and their formic acid solvates in formic acid and water

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Abstract

Problems associated with the determination of the solubilities of solvates and of nonsolvates which undergo phase transformation in the presence of an interacting solvent are discussed. When determining the solubility of a nonsolvate in an interacting solvent, a solvate may be formed resulting in a reduced equilibrium solubility corresponding to that of the solvate. Similarly, when determining the solubility of a solvate in a different solvent, a new solvate or the nonsolvate may be formed resulting in a reduced equilibrium solubility corresponding to that of the new phase. A useful extrapolation technique is developed to overcome the problems resulting from the solvation of nonsolvates in the solvent of crystallization and from the desolvation of solvates in water, often observed during the measurement of equilibrium solubilities by the equilibration method. A thermodynamic cycle analogous to Hess's law but based on free energies is used to predict the theoretical solubility of the solvates in water, especially those which are inaccessible by both the equilibration and the extrapolation methods. The model systems employed are 1,2-dialkyl-3-hydroxy-4-pyridones which form 1 : 1 formic acid solvates in the presence of formic acid and the 1 : 1 formic acid solvates which produce the corresponding unsolvated compound in the presence of water. There is good agreement between the solubility values measured by equilibration and derived from the extrapolation method and between those derived from the extrapolation method and calculated by means of the thermodynamic cycle.

Keywords: Cosolvency; Desolvation; Dialkylhydroxypyridone; Formic acid; Free energy of solution; Phase transition; Solubility; Solvate; Thermodynamic cycle

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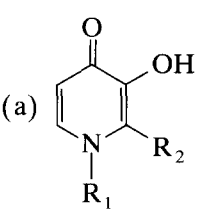
1. Introduction

Solubility is a critical physical quantity for the design and development of dosage forms with optimal properties. The solubility of a drug controls both the rate of dissolution and the amount of the drug that can be dissolved and frequently influences the bioavailability. Thus, an accurate estimate of solubility values is a necessary part of preformulation studies and assists in conferring desirable formulation, biopharmaceutical and distributive properties on the dosage form (Braxton and Rytting, 1989).

Solubility is generally determined by equilibrating an excess of the solid with the desired solvent at a constant, defined temperature. During solubility determinations the possibility of a phase change in the solid solute throughout the duration of the study should not be ignored. For example, the solvent molecule might become incorporated into the solute crystal lattice, resulting in the formation of a solvated crystal (Shefter and Higuchi, 1963; Pfeiffer et al., 1970) or the solvent molecule might be lost from the crystal lattice thereby producing a desolvated crystal (Chan et al., 1991). Both these phenomenon result in phase changes and hence the measured solubility values do not correspond to the true values for the original solid phase in the solvent that induces the phase change.

The main objective of the present work is to develop methods for determining the solubility of compounds which undergo a phase change due to solvation or desolvation in the presence of the solvent of interest. The compounds chosen for this study are 1,2-dialkyl-3-hydroxy-4-pyridones (DAHPs; Scheme 1) and their 1:1 formic acid solvates (DAHP-Fs). The representative DAHPs are 1,2-dimethyl-3-hydroxy-4-pyridone (DMHP), 1-propyl-2-methyl-3-hydroxy-4-pyridone (PMHP), 1-methyl-2-ethyl-3-hydroxy-4-pyridone (MEHP), and 1-propyl-2-ethyl-3-hydroxy-4-pyridone (PEHP). DAHPs are pharmaceutically important because of their ability to chelate iron when administered orally. There has been a recent thrust in the development of oral iron chelators due to the high cost of the only clinically approved iron chelator, desferrioxamine (DF). The therapeutic efficacy of DF is also compromised by its short half-life and the requirement for parenteral administration. The results of clinical trials indicate that DMHP is as effective as DF in chelating iron and is also efficacious and safe (Olivieri et al., 1989; Bartlett et al., 1990; Agarwal et al., 1991; Carnelli et al., 1992). Furthermore, in independent studies in animal models, PMHP and MEHP have also been shown to be effective oral iron chelators (Kontoghiorghes et al., 1986; Hider et al., 1990; Porter et al., 1990). For the purposes of the present study the DAHPs can undergo solvation, and the solvates can undergo desolvation, in the presence of appropriate solvents, either alone or when mixed with water.



	R_1	R_2	Compound
(a)	CH_3	CH_3	DMHP
	C_3H_7	CH_3	PMHP
	CH_3	C_2H_5	MEHP
	C_3H_7	C_2H_5	PEHP

(b) $H-C(=O)-OH$ Formic acid

Scheme 1. Molecular structures of (a) DAHPs and (b) formic acid.

The crystal structures of DMHP (Nelson et al., 1987; Chan et al., 1992), PMHP, MEHP, DMHP-F, PMHP-F and MEHP-F have already been published (Ghosh et al., 1993a). The solid state properties of DMHP, of the acetic acid solvate of DMHP (Chan et al., 1991), and of DMHP-F (Ghosh et al., 1990) have also been reported. The crystal structures of the aluminum and gallium complex of DMHP (Nelson et al., 1988) and of PMHP (Simpson et al., 1991) have been solved and show interesting hydrogen-bonding patterns. More recently, the influence of hydrogen-bond patterns and molecular structures of DAHPs and DAHP-Fs on the various thermodynamic quantities of these crystalline solids have been presented (Ghosh et al., 1993b).

2. Experimental

2.1. Preparation of DAHPs and DAHP-Fs

DAHPs were synthesized by the method outlined by Kontoghiorghes and Sheppard (1987, 1988). The solvents used for recrystallization of the DAHPs were water:ethanol mixture (1:1, v/v) for DMHP, methanol for MEHP and acetone for PMHP or PEHP. The formic acid solvates of DMHP and MEHP, designated as DMHP-F and MEHP-F respectively, were prepared by evaporating the excess of formic acid from a solution of the corresponding DAHP and formic acid (Fisher Scientific, Fairlawn, NJ). PMHP-F was prepared by evaporating the excess of formic acid from a formic acid + PMHP solution at low relative humidity in a desiccator containing phosphorus pentoxide (J.T. Baker Inc., Phillipsburg, NJ). PEHP-F was prepared by shaking an excess of PEHP in formic acid + water mixture (3:2, v/v) at 25°C for 24 h followed by slow cooling of the solution to 22°C. The nonsolvates (DAHPs) and the solvates (DAHP-Fs) were characterized by differential scanning calorimetry, thermogravimetric analysis, and by single crystal and powder X-ray diffractometry techniques, described by Chan et al. (1991, 1992), and by Ghosh et al. (1993a).

Purified water was obtained from the Millipore water purification system (Millipore Corp., Bedford, MA), ethanol (100%, USP grade) from Worum Chemical (St. Paul, MN), methanol ($\geq$ 99.8%, ACS, HPLC grade) from EM Science (Gibbstown, NJ) and acetone ($\geq$ 99.6%, ACS, analytical grade) from Mallinckrodt (St. Louis, MO).

2.2. Measurement of equilibrium solubilities

The equilibrium solubilities of the various solid forms, solvates and nonsolvates, were determined by adding an excess of the solid to the appropriate solvents, formic acid or distilled water, contained in glass scintillation vials of 20 ml capacity. All solubility measurements were performed in a temperature-controlled room maintained at 25.0 $\pm$ 0.2°C by circulating environmentally controlled air. In each case, a constant amount of the solid solute was added to a fixed volume of the solvent. Solubility equilibrium was judged to have been achieved when three consecutive 24 h UV-spectrophotometric readings described below differed by not more than 4%. After equilibration by agitation in a mechanical shaker (Labline Instruments Inc., IL), the saturated solutions were passed through poly(vinylidene fluoride) filters of pore size 0.22 μm (Millipore Corp., Bedford, MA) contained in a filtration unit (Millipore Corp.). The filtration unit, including the filter paper, was pre-equilibrated at 25°C to prevent precipitation of the solid from the equilibrated solution during filtration. In a few cases, aliquots of the saturated solution were centrifuged and the concentration of the supernatant analyzed. The concentrations obtained by either of the two methods, centrifugation of the aliquots or filtration of the concentrated solution, were in close agreement, indicating negligible adsorption onto the filter paper. The filtered solutions were appropriately diluted with distilled water and analyzed by UV spectrophotometry at λ_{max} = 276 nm (DU-50 spectrophotometer, Beckman Instruments Inc., Fullerton, CA). The molar absorptivity of the DAHPs was not influenced by formic acid over the concentration range employed. A small quantity of the solid phase in equilibrium with the saturated solution was removed, surface-dried using a filter paper, and analyzed by powder X-ray diffractometry to check for changes in the solid phases, if any, during the equilibration process.

2.3. Powder X-ray diffraction

Powder X-ray diffraction patterns were determined using an X-ray generator and a goniometer (model D-500, Siemens, Germany) with Cu K_α radiation at 30 mA and 45 kV with the diffraction angle, 2θ, increasing at a rate of 3° per min. Bragg-Brentano focusing geometry was used with a 1° incident aperture, 0.15° detector slit, and a scintillation counter as the detector. A single crystal graphite monochromator was used to enhance the signal to noise ratio. The samples were packed into an aluminum holder and the

patterns were recorded at $5° < 2\theta < 35°$, in increments of 0.05° at room temperature (22°C).

3. Results and discussion

3.1. Equilibrium solubilities of the solid phases

3.1.1. Equilibration method

The equilibrium solubilities of the four nonsolvates and their corresponding formic acid solvates in water and in formic acid (Table 1) were determined using the equilibration method described above. The solubility of each of the solvates in water is higher than that of the corresponding nonsolvate. However, the powder X-ray diffraction pattern of the solid phase remaining after equilibration of each solvate, DAHP-F, with water corresponded to that of the nonsolvate, DAHP (Fig. 1 in which DMHP and DMHP-F are representative examples). This observation indicates that each 1:1 solvate, DAHP-F, was desolvated to the corresponding nonsolvated and nonhydrated form of DAHP in contact with water. Therefore, the measured quantity is the solubility

Table 1
Apparent equilibrium solubilities of DAHPs and DAHP-Fs in water and in formic acid measured using the equilibration method at 25°C

Compounds	Solubility (mol/l) [a]	
	Water	Formic acid
DMHP	0.109 ± 0.006	2.92 ± 0.02 [b]
DMHP-F	0.894 ± 0.004 [c]	2.88 ± 0.02
PMHP	0.440 ± 0.008	4.22 ± 0.09 [b]
PMHP-F	2.28 ± 0.12 [c]	4.62 ± 0.16
MEHP	0.64 ± 0.03	3.27 ± 0.02 [b]
MEHP-F	1.86 ± 0.07 [c]	3.32 ± 0.03
PEHP	0.222 ± 0.004	2.81 ± 0.14 [b]
PEHP-F	1.23 ± 0.08 [c]	2.78 ± 0.18

[a] Mean ± SD ($n = 3$).
[b] Solvated in the presence of formic acid.
[c] Desolvated on contact with water.

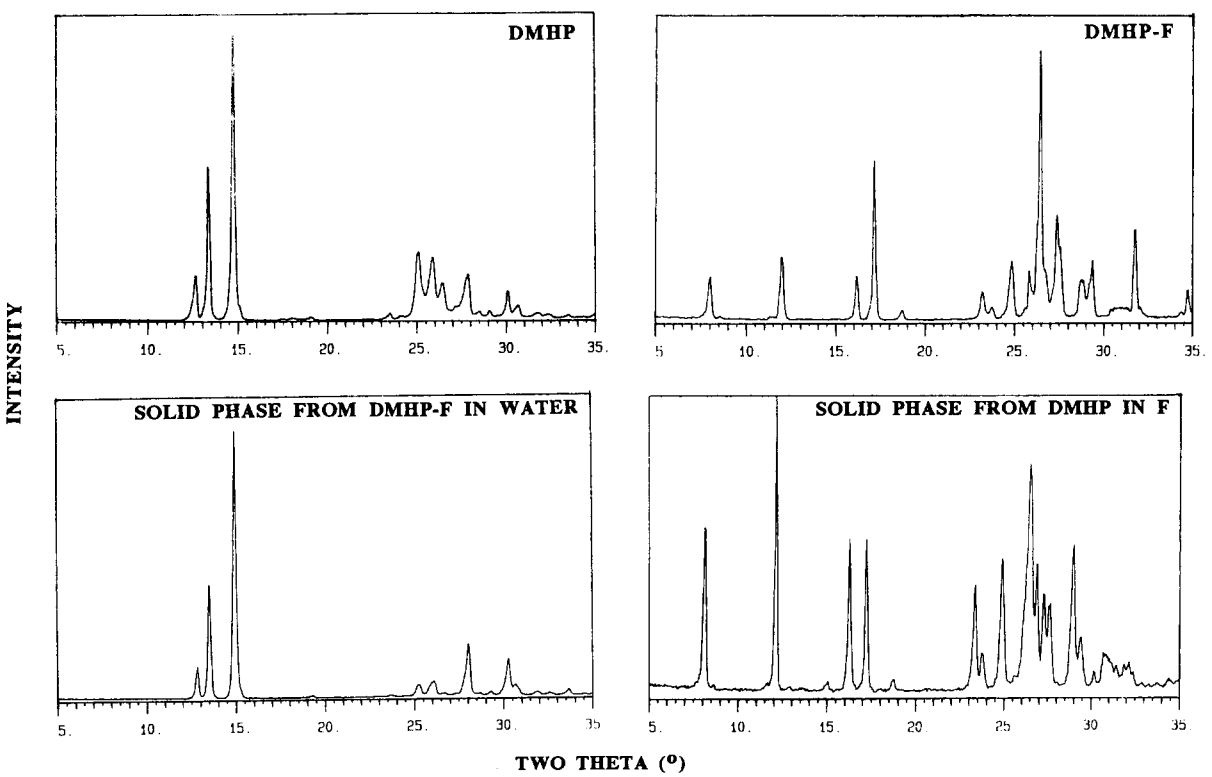


Fig. 1. Powder X-ray diffraction patterns of the different solid phases of DMHP and DMHP-F.

of the nonsolvate in formic acid + water mixture. The differences in the relative intensities of the powder X-ray diffraction peaks between members of each vertical pair in Fig. 1 may be attributed to preferred orientation. The presence of the formic acid released on dissolving each solvate has negligible effects on the pH of the saturated solutions and on the solubility of each DAHP, because the pK_a of formic acid (3.74 at 25°C; Budavari et al., 1989) is very similar to the pK_a of the hydroxyl group of each DAHP (3.3–3.7; Kontoghiorghes and Sheppard, 1988). Thus, the pH values of the saturated aqueous solutions are virtually identical, while formic acid and each DAHP are essentially unionized in water.

The measured solubilities of DAHPs and DAHP-Fs in formic acid are identical (Table 1). When DAHPs were placed in contact with formic acid, they rapidly dissolved but did not come into metastable equilibrium. The powder X-ray diffraction pattern of the solid phase remaining after equilibration of DAHPs in formic acid had peak 2θ values identical with those of the formic acid solvate (Fig. 1 in which DMHP and DMHP-F are representative examples). Thus, after a short time, the high solubility of the unsolvated DAHPs caused the solution to become supersaturated with respect to the solvate, DAHP-F, which was precipitated as crystals of the solvate. This finding suggests that, during the solubility measurements, each nonsolvate underwent solvation in the presence of formic acid to form DAHP-F, which is the stable phase in the presence of formic acid. Hence, the measured solubility is that of DAHP-F in formic acid and not that of DAHP in formic acid.

The previous two paragraphs indicate that it was not possible to measure directly the solubilities of the solvates in water or those of the nonsolvates in formic acid, because of the physical instability of the respective solid phases in the stated solvents. There was no such problem with the equilibrium solubility measurements of DAHPs in water or of DAHP-Fs in formic acid, since each of the solid phases was stable in contact with their saturated solutions in the respective solvents. The problems of solvation of DAHP in formic acid and of desolvation of DAHP-F in water during solubility measurements by the equilibration method were overcome by a useful extrapolation method described below.

3.1.2. Extrapolation prodcedure

This process utilizes the concept that the nature of the solid phase in equilibrium with its saturated solution is determined by the thermodynamic activity of the interacting solvent. In this case the formation of solvated crystals, DAHP-F, from nonsolvated crystals, DAHP, in the presence of formic acid, F, is represented by the following equilibrium:

$$\mathrm{DAHP}_{(\mathrm{solid})} + \mathrm{F} \overset{K}{\rightleftharpoons} \mathrm{DAHP\text{-}F}_{(\mathrm{solid})} \tag{1}$$

$$K = \frac{a_{\mathrm{DAPH\text{-}F,solid}}}{a_{\mathrm{DAHP,solid}} \cdot a_{\mathrm{F}}} \tag{2}$$

where the subscripts refer to the stated phases, K denotes the equilibrium constant, a_{F} is the activity of formic acid, while $a_{\mathrm{DAHP\text{-}F,solid}}$ and $a_{\mathrm{DAHP,solid}}$ represent the activities of DAHP-F and DAHP, respectively, in their solid phases.

According to Eq. 2, the solvated solid, $\mathrm{DAHP\text{-}F}_{(\mathrm{solid})}$, will be more stable than the nonsolvated solid, $\mathrm{DAHP}_{(\mathrm{solid})}$, when $K > 1$, i.e., when

$$a_{\mathrm{F}} > \frac{a_{\mathrm{DAHP\text{-}F,solid}}}{a_{\mathrm{DAHP,solid}} \cdot K} \tag{3}$$

The nonsolvate will be the more stable form in the inverse situation when $K < 1$. Thus, the solvation state of the compound will depend on the formic acid activity in the surrounding medium. Hence, by a judicious choice of formic acid activity, it should be possible to form the formic acid solvates in solution, if the situation represented by Eq. 3 is satisfied. The activity of formic acid may be changed by dilution of the liquid with a miscible cosolvent, such as water, which does not form a hydrate with the DAHP. If the solid-liquid reaction is not rate-limited, then below a certain formic acid activity the nonsolvate will exist in its native (nonsolvated) form, while above a certain activity of formic acid it will be converted to the formic acid solvate. This procedure also assures the stability of the formed solvate at the appropriate formic acid activity.

The solvent media employed for equilibrium

solubility measurements for the extrapolation method were 2, 4, 10, 20, 40 and 60% v/v formic acid in formic acid + water mixtures. A plot of solubility versus the volume percent of formic acid in water for DMHP, as the representative example, is shown in Fig. 2. Analogous results were obtained for the three other DAHP compounds. As expected, the addition of the cosolvent changes the solubility of the solute due to changes in intermolecular interactions in the solution (Yalkowsky and Valvani, 1977). The plot shows the following two regression lines: (a) an initial steep slope, which is linear (correlation coefficient, $r > 0.99$) over smaller values of volume percent of formic acid (0–10%) in water, and (b) a subsequent less steep slope which is linear ($r > 0.99$) at larger values of volume percent of formic acid (> 20%) in water.

The powder X-ray diffraction pattern (Fig. 1) of the solid phase represented by the steeper regression line in Fig. 2 corresponded to that of nonsolvated DMHP. Thus, this line represents the solubility profile of DMHP in formic acid + water mixtures. Extrapolation of this line to 0% formic acid (100% water) yields the theoretical solubility of DMHP in pure water and extrapolation to 100% formic acid (0% water) yields the theoretical solubility of DMHP in pure formic acid.

The powder X-ray diffraction pattern (Fig. 1) of the solid phase in equilibrium with the solution over the less steep regression line in Fig. 2 also suggests that the less steep regression line (≥ 20% formic acid) is the solubility profile of DMHP-F in formic acid + water mixtures. Hence, extrapo-

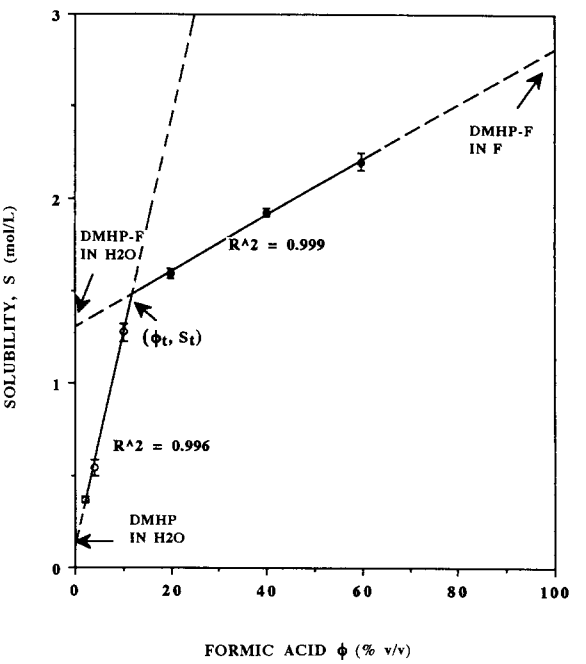


Fig. 2. Solubility of DMHP in formic acid (F) + water mixtures at 25°C, showing the transition point (ϕ_t,S_t).

Table 2
Comparison of the solubilities of DAHPs and DAHP-Fs determined by the equilibration and the extrapolation methods

Compounds	Solubility (mol/l) [a]			
	Water		Formic acid	
	Equilibration method	Extrapolation method	Equilibration method	Extrapolation method
DMHP	0.11 ± 0.01	0.11 ± 0.03	– [b]	11.7 ± 0.4
PMHP	0.44 ± 0.01	0.47 ± 0.03	– [b]	22.8 ± 0.5
MEHP	0.64 ± 0.03	0.69 ± 0.07	– [b]	31.8 ± 1.1
PEHP	0.22 ± 0.01	0.21 ± 0.07	– [b]	25.9 ± 1.8
DMHP-F	– [c]	1.30 ± 0.03	2.88 ± 0.02	2.52 ± 0.03
PMHP-F	– [c]	2.63 ± 0.04	4.62 ± 0.16	4.19 ± 0.04
MEHP-F	– [c]	– [d]	3.27 ± 0.02	– [d]
PEHP-F	– [c]	1.22 ± 0.08	2.78 ± 0.18	2.59 ± 0.08

[a] Mean ± SD ($n = 3$).
[b] Solvated during equilibration.
[c] Desolvated during equilibration.
[d] Not accessible by the extrapolation method because MEHP-F is not formed from formic acid in the presence of water.

lation of this line to 0% and 100% formic acid, as explained in the previous paragraph, gives the solubility of DMHP-F in water and in formic acid, respectively. The extrapolated solubility results are tabulated in Table 2 for all four DAHP, DAHP-F pairs. As shown in Table 2, analogous results were obtained for PMHP and PEHP in the formic acid + water system.

Table 2 shows good agreement between the solubilities determined by the extrapolation procedure and that using the equilibration method, thereby establishing the validity of the extrapolation method for the DAHPs under study. Other drug + water + cosolvent systems may give linear relationships with other functions of solvent compositions (Yalkowsky and Valvani, 1977), different from that shown in Fig. 2.

The formic acid solvate in each case has a higher aqueous solubility than the corresponding nonsolvate, presumably because the negative free energy of mixing of the released formic acid with water makes an additional contribution to the negative free energy of solution (Shefter and Higuchi, 1963; Grant and Higuchi, 1990). On the other hand, the solubility of the nonsolvate in formic acid is higher than that of the corresponding solvate, presumably because the negative free energy of solid solvation of the nonsolvate makes an additional contribution to the negative free energy of solution. Analogous behavior may be expected for the solvates of other organic compounds.

The solubility diagrams exemplified by Fig. 2 indicate the ranges of solvent composition in which each solvate and its nonsolvate are stable. Such changes in solubility with changes in solvent composition along a straight line refer to an equilibrium between a solid phase of definite unchanging composition (solvate or the nonsolvate) and a solution of changing properties (different volume percent of formic acid in binary mixtures with water). The concentration of the solute in solution at equilibrium, i.e., the solubility values of either the solvate or the nonsolvate, may vary as the composition of the solvent changes, while the activity of the crystallizing molecular species is equal to that of the crystalline form present (Pfeiffer et al., 1970). The plots (Fig. 2) of the solubility of each solvate and of the corresponding nonsolvate versus the solvent composition (formic acid + water) intersect at the phase transition point (ϕ_t,S_t) between the solvate and the nonsolvate. ϕ_t is the volume percent of formic acid at the transition point, whereas S_t denotes the solubility which is the same for each solid phase at the transition point. At this point, the nonsolvate is in equilibrium with the solvate and the saturated solution. Therefore, at this point the nonsolvate can be reversibly converted to the solvate and vice versa. At the phase transition point, both the solvate and the corresponding nonsolvate coexist at equilibrium at the same solvent composition (ϕ_t) and hence have the same solubility (S_t). At other solvent compositions, the more soluble solid phase is necessarily metastable with respect to the less soluble solid phase.

The above considerations apply to all DAHP, DAHP-F pairs with the exception of MEHP, MEHP-F. Although MEHP was converted to MEHP-F in pure formic acid, it did not form MEHP-F in any aqueous mixtures containing up to 90% (v/v) formic acid. Hence, it was not possible to obtain the solubility profile of MEHP-F in formic acid + water mixtures (the regression line in Fig. 2 at higher volume percent of formic acid) even though it was possible to obtain the solubility profile of MEHP in formic acid + water mixtures (the regression line in Fig. 2 at lower volume percent of formic acid). From the latter regression line the solubilities of MEHP in water and in formic acid were obtained by extrapolation to 0% and 100% formic acid, respectively. Since MEHP did not form a 1:1 formic acid solvate (MEHP-F) in formic acid + water mixture, a thermodynamic cycle, described below, was employed to determine the theoretical solubility of MEHP-F in water.

3.2. Thermodynamic cycle

Since the free energy changes involved in the various solution processes are thermodynamic state functions, they may be added or subtracted to calculate the free energy of the solution process corresponding to the otherwise inaccessible solubility of MEHP-F in water. This procedure

requires calculation of the free energy changes involved in the following equilibrium processes (Chan et al., 1991):

(1) Solution of the nonsolvate (MEHP) in water;
(2) Solution of the solvate (MEHP-F) in formic acid;
(3) Solution of the nonsolvate (MEHP) in formic acid;
(4) Mixing of formic acid (F) with water;
(5) Solution of the solvate (MEHP-F) in water.

Expressions for the standard Gibbs free energy changes associated with each of the above processes are given in Table 3. The standard state of unit activity of each solute is defined as a hypothetical 1 mol/l solution which is assumed to behave as if it were infinitely dilute. The subscripts refer to the phase of the corresponding species; e.g., $MEHP_{(solid)}$ represents MEHP in the solid phase, while $MEHP_{(aq)}$ corresponds to MEHP in the aqueous phase. R is the universal gas constant, T denotes the temperature of measurement (298.15 K), $\mu_{MEHP,solid}$ and $\mu_{MEHP\text{-}F,solid}$ represent the chemical potentials of MEHP and MEHP-F, respectively, each in the solid phase, and the square brackets indicate the molar concentrations of the particular species. Thus, the standard Gibbs free energy changes for the first three steps are calculated from the logarithms of the solubilities of MEHP in water, $[MEHP]_{aq}$, MEHP-F in formic acid, $[MEHP\text{-}F]_F$, and of MEHP in formic acid, $[MEHP]_F$.

The standard Gibbs free energy for the mixing of formic acid with water in step 4 (above and in Table 3) is obtained from the activity coefficient of formic acid at infinite dilution in water, $\gamma^{\infty}_{F,aq}$. This quantity was based on the molarity scale at 298.15 K (25°C), the standard state being the pure liquid formic acid. However, only the mole fraction based value of $\gamma^{\infty}_{F,aq}$ (0.74) has been reported (Gmehling and Onken, 1977). This value was derived from partial vapor pressure measurements above binary mixtures of formic acid + water (Udovenko and Aleksandrova, 1960) at 303.15 K (30°C), and was correlated using the van Laar (1910) equations. The influence of the 5 K difference in temperature on the value of $\gamma^{\infty}_{F,aq}$ is assumed to be insignificant. However, since the standard state of each solute in steps 1–3 and 5 (above and in Table 3) is a hypothetical 1 mol/l solution, the same standard state must be applied to this calculation in step 4. Hence, $\gamma^{\infty}_{F,aq}$ was converted to the molarity scale by multiplying by the molar volume of water (0.0180885 l/mol at 303.15 K). Thus, the value $\gamma^{\infty}_{F,aq} = 0.01337$ l/mol at 303.15 K was employed in step 4.

Since free energy is a thermodynamic state function, the standard Gibbs free energy for the dissolution of MEHP-F in water (step 5) can be calculated by adding steps 1, 2 and 4 and subtracting step 3, as shown in Table 3:

$$\Delta G^{\circ}_{MEHP\text{-}F,aq} = \Delta G^{\circ}_{MEHP,aq} + \Delta G^{\circ}_{MEHP\text{-}F,F} - \Delta G^{\circ}_{MEHP,F} + \Delta G^{\circ}_{F,aq} \quad (4)$$

The numerical values of the standard Gibbs free energy changes for each of the above pro-

Table 3
Standard Gibbs free energy changes for the various solution processes involving MEHP and its formic acid solvate

Solution processes			Free energy change (kJ/mol)		
(1) $MEHP_{(solid)}$	$\rightleftharpoons$	$MEHP_{(aq)}$	$\Delta G^{\circ}_{MEHP,aq} - \mu_{MEHP,solid}$	$= -RT\ln[MEHP]_{aq}$	$= 1.09 \pm 0.12$ [a]
(2) $MEHP\text{-}F_{(solid)}$	$\rightleftharpoons$	$MEHP_{(F)}$	$\Delta G^{\circ}_{MEHP\text{-}F,F} - \mu_{MEHP\text{-}F,solid}$	$= -RT\ln[MEHP\text{-}F]_F$	$= -2.94 \pm 0.02$ [a]
(3) $MEHP_{(solid)}$	$\rightleftharpoons$	$MEHP_{(F)}$	$\Delta G^{\circ}_{MEHP,F} - \mu_{MEHP,solid}$	$= -RT\ln[MEHP]_F$	$= -8.57 \pm 0.09$ [a]
(4) $F_{(F)}$	$\rightleftharpoons$	$F_{(aq)}$	$\Delta G^{\circ}_{F,aq}$	$= RT\ln(\gamma^{\infty}_{F,aq})$	$= -10.8 \pm 0.12$ [b,c]
(5) $MEHP\text{-}F_{(solid)}$	$\rightleftharpoons$	$MEHP_{(aq)} + F_{(aq)}$	$\Delta G^{\circ}_{MEHP\text{-}F,aq} = \Delta G^{\circ}_{MEHP,aq} + \Delta G^{\circ}_{MEHP\text{-}F,F} - \Delta G^{\circ}_{MEHP,F} + \Delta G^{\circ}_{F,aq}$	$= -2RT\ln[MEHP\text{-}F]_{aq} + \mu_{MEHP\text{-}F,solid}$	$= -4.08 \pm 0.19 + \mu_{MEHP\text{-}F,solid}$ (calculated)

[a] SD was calculated by the theory of propagation of errors (Livingston, 1943; Topping, 1963).
[b] $(\gamma^{\infty}_{F,aq})$ was calculated from Gmehling and Onken (1977), Udovenko and Aleksandrova (1960), and Van Laar (1910).
[c] SD was calculated by the theory of propagation of errors, assuming a somewhat arbitrary 5% error in $(\gamma^{\infty}_{F,aq})$ for the purposes of evaluation of error of the derived quantity, $\Delta G^{\circ}_{F,aq}$. The assumed error is probably greater than the actual error.

Table 4
Comparisons of the standard free energy changes and the equilibrium solubilities of DAHP-Fs in water determined by the extrapolation method and the thermodynamic cycle

Compound	Extrapolation method		Thermodynamic cycle	
	Solubility [a] (mol/l)	Free energy change [b] (kJ/mol)	Free energy change [b] (kJ/mol)	Solubility [b] (mol/l)
DMHP-F	1.30 ± 0.03	−1.32 ± 0.12	−1.79 ± 0.20	1.43 ± 0.06
PMHP-F	2.63 ± 0.04	−4.79 ± 0.08	−4.76 ± 0.17	2.61 ± 0.08
MEHP-F	– [c]	– [c]	−4.08 ± 0.19	2.27 ± 0.09
PEHP-F	1.22 ± 0.08	−0.98 ± 0.32	−1.49 ± 0.27	1.35 ± 0.07

[a] Mean ± SD ($n = 3$).
[b] SD was calculated by the theory of propagation of errors (Livingston, 1943; Topping, 1963).
[c] MEHP does not form a solvate in formic acid + water mixture containing up to 90% (v/v) formic acid.

cesses involving MEHP and MEHP-F are listed in Table 3. The standard Gibbs free energy of solution of MEHP in formic acid ($\Delta G^{\circ}_{MEHP,F} = -8.6$ kJ/mol) is a negative quantity with respect to the chemical potential of solid MEHP, indicating an appreciable thermodynamic driving force for conversion of solid MEHP to the solution, $MEHP_{(F)}$ (Table 3). Similar negative free energy changes were also obtained for the other three solvates ($\Delta G^{\circ}_{DMHP,F} = -6.1$ kJ/mol; $\Delta G^{\circ}_{PMHP,F} = -7.8$ kJ/mol; $\Delta G^{\circ}_{PEHP,F} = -8.1$ kJ/mol).

The free energy of solution of MEHP-F in water calculated using the thermodynamic cycle (Table 3) and Eq. 4 is −4.08 kJ/mol. From this value the solubility of MEHP-F in water was calculated (2.27 mol/l) as shown in step 5. The thermodynamic cycle was also used to calculate the free energies, and hence the solubilities, of the other three solvates in water and the results are compared with those obtained from the extrapolation method in Table 4. Table 4 shows good agreement between the respective aqueous solubilities of DMHP-F, PMHP-F or PEHP-F predicted using the thermodynamic cycle and those determined by the extrapolation procedure. This agreement lends confidence to the calculated value of the solubility of MEHP-F mentioned above. The small difference between the solubilities obtained from the thermodynamic cycle and the extrapolation method can be partially attributed to the fact that the free energy change in step 4 (Table 3) was calculated from activity coefficients measured at 303.15 K (Udovenko and Aleksandrova, 1960) instead of at 298.15 K, the

Table 5
Free energy of solid solvation, ΔG°_{solv}, and equilibrium constant, K, for the formation of the solvate from the nonsolvate calculated from the molar solubilities or from the transition points (ϕ_t,S_t), where ϕ_t is the volume percent of formic acid in water

Compound	ΔG°_{solv} (kJ/mol) [a]	K (mol/l) [a,b]	ϕ_t (%, v/v) [c]	K (mole fraction) [c,d]
DMHP → DMHP-F	−3.53 ± 0.09	4.15 ± 0.06	11.72 [e]	22.71
PMHP → PMHP-F	−3.98 ± 0.10	4.98 ± 0.06	10.48 [e]	25.54
MEHP → MEHP-F	−5.64 ± 0.09	9.73 ± 0.04	4.54 [f]	60.90
PEHP → PEHP-F	−5.40 ± 0.24	8.83 ± 0.08	4.13 [e]	68.25

[a] SD was calculated by the theory of propagation of errors (Livingston, 1943; Topping, 1963).
[b] K is the equilibrium constant on a molar concentration (mol/l) scale for formation of the solvate from the nonsolvate in the solid state, calculated from the solubilities according to Eq. 6, with $a_F = 1$.
[c] SD could not be calculated because both the predictor and the response were calculated from the transition point.
[d] K is the equilibrium constant on a mole fraction scale for formation of the solvate from the nonsolvate in the solid state, calculated from ϕ_t at the transition point according to Eq. 7, with $a_F = \gamma_F \cdot x_F$.
[e] Determined experimentally.
[f] Calculated theoretically as explained under section 3.3.

temperature of measurement for all other solubility values.

3.3. Transition point

The transition point (ϕ_t,S_t in Fig. 2) has been defined as the point at which the two lines corresponding to the solubilities of a given DAHP and of its solvate, DAHP-F, intersect and at which the nonsolvate is converted to the solvate and vice versa in the formic acid + water mixtures. MEHP does not form MEHP-F in formic acid + water mixtures containing up to 90% (v/v) of formic acid, as explained previously. Hence, it is not possible to plot the second regression line for MEHP, for which the intersection with the first regression line would have provided an experimental value of ϕ_t. However, a theoretical second regression line for MEHP can be drawn as a straight line between the points corresponding to the solubility of MEHP-F in water (0% formic acid, measured using the thermodynamic cycle) and that of MEHP-F in formic acid (100% formic acid, measured using the equilibration technique). Intersection of this line with the first regression line then gives the theoretical value of ϕ_t for MEHP which is shown in Table 5.

The transition point (ϕ_t,S_t in Fig. 2) indicates the affinity or the driving force of the nonsolvate to form the solvate and hence can be related to free energy of solid solvation. The free energy of solid solvation (Grant and Higuchi, 1990) of the nonsolvates, DAHPs, according to the equilibrium:

$$\mathrm{DAHP}_{(\mathrm{solid})} + \mathrm{F} \overset{K}{\rightleftharpoons} \mathrm{DAHP\text{-}F}_{(\mathrm{solid})} \qquad (5)$$

is given by

$$\Delta G_{\mathrm{solv}} = -RT \ln K = -RT \ln \frac{[\mathrm{DAHP}]_{\mathrm{F}}}{[\mathrm{DAHP\text{-}F}]_{\mathrm{F}}} \qquad (6)$$

where $[\mathrm{DAHP}]_{\mathrm{F}}$ is the solubility of DAHP in the formic acid and $[\mathrm{DAHP\text{-}F}]_{\mathrm{F}}$ denotes the solubility of DAHP-F in the formic acid. $[\mathrm{DAHP}]_{\mathrm{F}}$ was determined by the extrapolation method and $[\mathrm{DAHP\text{-}F}]_{\mathrm{F}}$ was measured using the equilibration procedure.

Since ΔG_{solv} indicates the affinity of the compounds to form the solvates, a compound for which ΔG_{solv} is a larger negative quantity will have a larger driving force to form the solvate and hence will form the solvate at a lower volume percent of formic acid giving rise to a lower ϕ_t value. These conclusions are summarized in Table 5. Thus, MEHP and PEHP, which have higher affinities for formic acid than do DMHP and PMHP for the formation of the solvate (larger negative values for $\Delta G^{\circ}_{\mathrm{solv}}$), have lower ϕ_t values. Moreover, the ϕ_t values parallel the $\Delta G^{\circ}_{\mathrm{solv}}$ values; ϕ_t values for DMHP and PMHP are similar and significantly different from those of MEHP and PEHP ($\Delta G^{\circ}_{\mathrm{solv}}$ for DMHP and PMHP are similar and significantly different from those of MEHP and PEHP, which have similar $\Delta G^{\circ}_{\mathrm{solv}}$ values).

The equilibrium constant, K, for the formation of each formic acid solvate is given by Eq. 2. At the transition point (ϕ_t,S_t) in Fig. 2 and in Table 5, the activities of the solvate and of the nonsolvate are equal, i.e., $a_{\mathrm{DAHP\text{-}F,solid}} = a_{\mathrm{DAHP,solid}}$, therefore:

$$K = \frac{1}{a_{\mathrm{F}}} = \frac{1}{\gamma_{\mathrm{F,aq}} \cdot x_{\mathrm{F}}} \qquad (7)$$

where a_{F} is the activity of formic acid at the transition point, x_{F} represents the mole fraction of formic acid at the transition point and $\gamma_{\mathrm{F,aq}}$ is the activity coefficient of formic acid in water based on the mole fraction scale, the standard state of unit activity of formic acid being pure liquid formic acid. The mole fraction of formic acid was calculated from the volume fraction of formic acid assuming that the partial molar volume of formic acid in water is equal to the molar volume of pure formic acid. This assumption implies that there is no change in volume due to mixing of formic acid with water. Since both formic acid and water self-associate by hydrogen bonding and mutually interact by the same mechanism, this assumption is not likely to introduce major errors. The fact that the value of $\gamma^{\infty}_{\mathrm{F,aq}}$ (0.74) is not far from unity supports this assumption and suggests that $\gamma_{\mathrm{F,aq}}$ may be set equal to $\gamma^{\infty}_{\mathrm{F,aq}} = 0.74$. The K values for DMHP, PMHP, MEHP and PEHP, calculated using Eq. 7 with

the above assumptions and based on the mole fraction scale, are stated in Table 5.

The K values were also calculated according to Eq. 6. These values are based on the molarity scale (mol/l) for DAHP and DAHP-F, the standard state of unit activity of these substances in Eq. 6 being a hypothetical 1 mol/l solution which is assumed to behave as it were infinitely dilute. This equation requires that formic acid be in the pure state for which the activity of formic acid, $a_F = 1$. The K values so calculated are also presented in Table 5.

The K values calculated using either Eq. 7 or 6 give different but comparable results. Specifically, MEHP and PEHP have similar values of K, while DMHP and PMHP have similar but lower values of K than the former pair of compounds. Thus, MEHP and PEHP are more readily solvated by formic acid than are DMHP and PMHP. Although MEHP does not form MEHP-F in formic acid + water mixtures containing up to 90% (v/v) formic acid, the value of K is not smaller than that for the other three compounds in Table 5. This result suggests that the inability of MEHP to form MEHP-F in the investigated range of formic acid + water mixtures is probably not due to thermodynamic factors but rather to kinetic factors.

4. Conclusions

(1) A useful extrapolation procedure was developed to determine the solubilities of DAHPs and of DAHP-Fs in water and in formic acid. This was necessary to overcome the problem of solvation of DAHP in formic acid and that of desolvation of DAHP-F in water.

(2) A thermodynamic cycle was employed to predict the solubilities of DAHP-Fs in water. This method may be generally applicable whenever the solubilities are inaccessible by either the equilibration or the extrapolation procedure.

(3) When more than one solubility method is applicable, there is good agreement between the solubilities determined by the equilibration and the extrapolation methods and between the solubilities determined by the extrapolation method and the thermodynamic cycle.

(4) The equilibrium constant, K, for the solid state solvation of each DAHP was calculated in terms of either the mole fraction or the molarity scale, using appropriate, but different, standard states. According to either criterion, the K values indicate an approx. 2-fold greater solvating tendency for MEHP or PEHP than for DMHP or PMHP.

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