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Thermodynamics of Fenoxycarb in Solution

Manuel Kuhs\textsuperscript{a*}, Michael Svärd\textsuperscript{b} and Åke C. Rasmuson\textsuperscript{ab}
\textsuperscript{a} Department of Chemical and Environmental Science, Materials and Surface Science Institute, University of Limerick, Limerick, Ireland.
\textsuperscript{b} Department of Chemical Engineering and Technology, KTH Royal Institute of Technology, Stockholm, Sweden.
\* Corresponding author at: Department of Chemical and Environmental Science, Materials and Surface Science Institute, University of Limerick, Limerick, Ireland. Tel.: +353 86 386 6783
E-mail address: manuel.kuhs@ul.ie (Manuel Kuhs)

Abstract

The solubility of fenoxycarb has been determined between 278 and 318 K in several organic solvents. The solid phase at equilibrium and some indication of polymorphism has been properly examined by powder XRD, DSC, Raman and ATR-FTIR spectroscopy, solution $^1$H NMR and SEM. Using literature data the activity of the solid phase within a Raoult’s law definition has been calculated, based on which solution activity coefficients have been estimated. In ethyl acetate, the van’t Hoff enthalpy of solution is constant over the temperature range and equals the melting enthalpy. However, it is shown that the solution is slightly non-ideal with the heat capacity difference term compensating for the activity coefficient term. In toluene, the van’t Hoff enthalpy of solution is constant as well but clearly higher than the melting enthalpy. In methanol, ethanol and isopropanol, van Hoff curves are strongly non-linear, the slope however clearly approaching the melting enthalpy at higher temperatures. In all solvents, positive deviations from Raoult’s law are prevailing. The activity coefficients follow a decreasing order of isopropanol > ethanol > methanol > toluene > ethyl acetate, and in all solvents decrease monotonically with increasing temperature. The highest activity coefficient is about 18 corresponding to about 2.5 kJ/mol of deviation from ideality.

Keywords

solubility, activity, activity coefficient, van’t Hoff enthalpy, ideal solution, heat capacity
1 Introduction

Prediction of melting point and solubility of a compound is of high interest in pharmaceutical research since it has a significant influence on the bioavailability of drugs and provides a basis for process design. Industrial crystallization processes, considered the single most important unit operation in the pharmaceutical industry [1] because over 90% of all pharmaceutical products contain crystalline ingredients [2], often require accurate knowledge of the solubility and melting point of the crystalline material or its precursors. Measuring solubility is not only time-consuming but also notoriously difficult, with inconsistencies in reported data existing even within the paper in which the data is published [3]. Melting points are sometimes impossible to measure experimentally when the solid phase of interest is metastable or becomes metastable (enantiotropy) at higher temperatures [4; 5].

Thus, many techniques are being developed to predict solubility and melting point, though none are as yet sufficient to replace experimental work for accurate data [6]. A common method for estimating melting temperature is through linear extrapolation of solubility data in a van’t Hoff plot, which assumes ideal solution behaviour and negligible heat capacity difference between solid and melt [7]. More complex methods include classical Quantitative Structure-Property Relationship (QSPR) modelling[8], group contribution methods [9] and correlating similar compounds [10]. Prediction of the solubility at different temperatures is done by the Hildebrand-Scatchard models [11], as well as several methods that involve experimentally obtaining one or more solubility data points [6; 12]. As expected, the latter are far more accurate, with one method’s modelled solubility matching the real solubility within 5 K on average [6], while the former deviate on average by 150% [12]. Some of these methods also assume ideal solution behaviour and negligible heat capacity differences between solid and melt, while a recent one includes activity coefficients estimation [6].

Fenoxycarb is an insect growth regulator with juvenile hormone activity [13]. It has chemical formula C_{17}H_{19}NO_{4} and systematic name 2-(p-phenoxyphenoxy)ethylcarbamate. The molecular structure, Figure 1, shows significant similarity to some pharmaceutical molecules, e.g. fenofibrate. Its melting
temperature and enthalpy are reported as 326.31 K and 26.98 kJ mol$^{-1}$, respectively [14]. To our knowledge, the only previously reported solubility data is for water at 293.15 K (viz. 0.006 g / kg) [15]. Here, we report careful measurement of the solubility in several organic solvents. Using published calorimetric data [14] of melting properties and solid and melt heat capacities, we have rigorously calculated the ideal solubility, which is then used to estimate activity coefficients of fenoxycarb in the different solvents over the measured temperature range.

The solubility reflects the equilibrium situation between two different phases: the solute as a solid phase and the solute in solution. At least one third of all organic compounds are polymorphic, i.e. they can form different crystals structures. Since the physical properties differ for polymorphs of the same compound, the solubility of a compound depends on the polymorph, and it is vital that solubility measurements are associated with a proper identification and control of the solid phase [16; 17]. Accordingly, this paper also contains an investigation of the solid phase for which the solubility data is determined, and some concerns about possible polymorphism are carefully analysed. To our knowledge only one crystal form of fenoxycarb has been reported, and recently we reported its structure for the first time [18].

![Figure 1. Fenoxycarb.](image-url)
2 Experimental

The purities and suppliers of all chemicals are reported in Table 1. All materials are used directly without further purification. Fenoxycarb is received as a large, congealed mass; no amorphous content was found by powder x-ray diffraction.

Table 1. Source and mass fraction purity of chemicals.

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Source</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoxycarb</td>
<td>Syngenta, Switzerland</td>
<td>0.988</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>VWR</td>
<td>0.997</td>
</tr>
<tr>
<td>Methanol</td>
<td>Sigma-Aldrich</td>
<td>0.999</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Sigma-Aldrich</td>
<td>0.998</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>Sigma-Aldrich</td>
<td>0.997</td>
</tr>
<tr>
<td>Toluene</td>
<td>Sigma-Aldrich</td>
<td>0.999</td>
</tr>
</tbody>
</table>

2.1 Solubility

Solubility was determined using a modified form of a gravimetric technique previously described [16; 19] which is considered to be one of the most accurate methods for measuring solubility [3]. Solutions saturated at predetermined temperatures between 278 and 318 K were created by adding an excess of solid fenoxycarb to a solvent in a sealed vial (30 ml, PTFE/EDPM screw cap), equipped with a magnetic stirring bar (0.5 x 0.128 in), placed on top of a submersible magnetic stirring plate (2Mag) in a temperature-controlled water bath (Grant GR150, stability ± 0.005 K and uniformity ± 0.02 K at 310 K). The temperature of the water bath was measured with a calibrated digital thermometer (Dostmann P650, accuracy ±0.03 K). The solutions were stirred for 12 hours at 400 rpm, followed by a 6 hour settling period during which the stirring was turned off. Syringes (5 ml) and syringe filters (0.2 µm PTFE) were pre-heated/cooled to the same temperature as the water bath. These were then used to filter ~0.5 ml of the supernatant into pre-weighed glass vials, which were quickly sealed to
prevent evaporation. The vials were weighed, uncovered and placed in a fume hood for solvent evaporation, weighed regularly until fully dried (< 0.1% mass loss over 48 hours) and the solubility calculated. The balance used had an accuracy of ±0.0001 g. To test the repeatability of achieving an equilibrated solution, the solubility at 278, 283 and 288 K was determined in duplicate. The repeatability of the filtration and drying processes was tested by filtering and drying the 293, 303 and 313 K supernatants in duplicate. The concentration of a known solution of fenoxycarb in isopropanol was also determined by the same gravimetric method and differed only 0.25% from the known concentration.

To verify that 12 hours dissolution is sufficient to achieve equilibrium, saturation was also approached from supersaturation as follows. The solutions were heated 10 K above the desired temperature and stirred for 12 hours, allowing most of the excess solid to dissolve. The water bath was then set to the desired temperature, and the solutions left stirring at this temperature for 12 hours. The solids were allowed to settle for 6 hours and the supernatant analysed as above. This was done only for the lowest temperature analysed (i.e. 5 K) since it was presumed that reaching equilibrium would be slowest at this temperature.

2.2 Solid Phase Characterisation

A ¼ inch diameter immersion probe attached to a Kaiser RamanRxn2 Analyzer with an Invictus 785 nm NIR laser set to 100 mW was used to obtain the Raman IR spectra of the solutions and undissolved solids used in 2.1 by direct insertion of the probe into the vials. iC Raman software, version 4.1, was used to collect the spectra from 150 – 3,400 cm⁻¹ with an exposure time between 15 and 45 s (calibrated for each sample to give a pixel fill of around 50% at the detector), 3 accumulations, a resampling interval of 1 cm⁻¹, cosmic ray removal and intensity correction. Solvent subtraction yielded the spectra of the dissolved and undissolved fenoxycarb.

Before drying and without any sample preparation, the excess solids (in the form of slurries) were removed from the solubility vials using a spatula and placed on a PerkinElmer Universal ATR Sampling Accessory attached to a PerkinElmer Spectrum 100 FT-IR instrument. The IR spectrum
between 600 and 4,000 cm\(^{-1}\) was collected using 4 background-subtracted co-added scans. The samples were then dried and ground using a mortar and pestle and analysed again by ATR-FTIR. Filtration could not be used during the drying process because clogging of the pores would occur due to the thickness of the slurry, and so unaided air drying at room temperature (because of the low melting point of fenoxycarb and to prevent any potential phase transformation) was employed.

Dried samples both before and after grinding were spin-coated with gold and analysed using a JEOL CarryScope Scanning Electron Microscope JCM-5700. Dried, ground samples were also placed on a silicon crystal zero-background disc, smoothed using a glass slide and then analysed using a Phillips PANalytical X’Pert MPD Pro with PW3064 sample spinner using a Cu K\(\alpha\) source (\(\lambda = 1.5418\) Å), nickel filter, fixed divergence slit of 1/2°, and accelerating voltage and anode current of 40 kV and 35 mA, respectively. Data was collected from 5 – 70 °2\(\theta\) in steps of 0.0167 ° at a rate of 19.685 s per step and a sample rotation of 15 rpm using PANalytical Data Collector, version 2.0.

The same samples were then checked for presence of solvent or impurities using a JEOL JNM-GSX 270 FT Nuclear Magnetic Resonance (NMR) instrument by dissolving them in deuterated chloroform (99.8% deuteration, 0.03% TMS, VWR BDH Prolabo) and carrying out \(^1\)H solution NMR at 270 MHz.

Using a PerkinElmer Pyris I Differential Scanning Calorimetry (DSC) instrument, the thermal properties of the dried, ground samples were measured by placing around 5 mg of a sample into a 40 \(\mu\)l aluminium pan without holes, which was then sealed by a 30 \(\mu\)l aluminium lid with holes and placed into the sample holder. The reference pan consisted of the same two aluminium pans without sample. The sample was heated from 288.15 to 343.15 K at a rate of 1 K/min (the first cycle), cooled back to 288.15 K at 100 K/min, held at that temperature for 10 minutes and then reheated to 343.15 K at 1 K/min (the second cycle). After baseline subtraction, the melting point (extrapolated onset temperature) and enthalpy of fusion were calculated.
The Kaiser RamanRxn2 Analyzer was then used to obtain the Raman spectra of the dried, ground samples. Operating conditions were the same as above except using an MR Probe in an enclosed sample container for non-contact analysis instead of an immersion probe.

3 Results & Discussion

3.1 Solubility

The solubility of fenoxycarb in various organic solvents at different temperatures is presented in Table 2 (as mole fraction) and shown graphically in Figure 2 (as g/g solvent). Values obtained by approaching saturation from supersaturation did not show any significant difference, confirming that the values in Table 2 represent the true equilibrium solubility at the given temperatures. The low CVs for the 278 K, 283 K and 288 K data confirm that achieving equilibrium is reproducible, while the low CVs at 293 K, 303 K and 313 K verify the repeatability of the drying process (see 2.1). Clearly the solubility is very high in all these solvents, partly reflecting that the temperature range is close to the melting point of fenoxycarb.

Table 2. Mole fraction solubility ($x_{eq}$) of fenoxycarb at temperature $T$ in various solvents, along with standard uncertainties $u(x)$.

<table>
<thead>
<tr>
<th>T (K)</th>
<th>Methanol</th>
<th>Ethanol</th>
<th>Isopropanol</th>
<th>Ethyl Acetate*</th>
<th>Toluene*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$x_{eq}$</td>
<td>$u(x)$</td>
<td>$x_{eq}$</td>
<td>$u(x)$</td>
<td>$x_{eq}$</td>
</tr>
<tr>
<td>278.17</td>
<td>0.0188</td>
<td>0.00018</td>
<td>0.0195</td>
<td>0.00002</td>
<td>0.0121</td>
</tr>
<tr>
<td>283.14</td>
<td>0.0298</td>
<td>0.00003</td>
<td>0.0287</td>
<td>0.00026</td>
<td>0.0175</td>
</tr>
<tr>
<td>288.17</td>
<td>0.0551</td>
<td>0.00023</td>
<td>0.0440</td>
<td>0.00017</td>
<td>0.0288</td>
</tr>
<tr>
<td>293.15</td>
<td>0.1196</td>
<td>0.00019</td>
<td>0.0798</td>
<td>0.00003</td>
<td>0.0504</td>
</tr>
<tr>
<td>298.14</td>
<td>0.2151</td>
<td>0.00073</td>
<td>0.1578</td>
<td>0.00009</td>
<td>0.1081</td>
</tr>
<tr>
<td>303.1</td>
<td>0.3693</td>
<td>0.00794</td>
<td>0.2969</td>
<td>0.00054</td>
<td>0.2612</td>
</tr>
<tr>
<td>308.06</td>
<td>0.4654</td>
<td>0.00119</td>
<td>0.4354</td>
<td>0.00062</td>
<td>0.4242</td>
</tr>
<tr>
<td>313.15</td>
<td>0.6426</td>
<td>0.00479</td>
<td>0.6151</td>
<td>0.00590</td>
<td>0.6054</td>
</tr>
<tr>
<td>317.8</td>
<td>0.7548</td>
<td>0.01195</td>
<td>0.7348</td>
<td>0.00872</td>
<td>0.7409</td>
</tr>
</tbody>
</table>

* Solubilities at 298.14, 308.06 and 317.8 K were only determined for the alcohols as the temperature dependence is most marked in these solvents.

† Standard uncertainty $u(T) = 0.055$ K.

‡ At 292.99 K.
Nordström and Rasmuson [6] evaluated different regression models for the solubility of various organic solutes in organic solvents, and found that in most cases a simple two- or three-parameter equation suffices to obtain a good fit to the data. However, it is found that for fenoxycarb in the solvents evaluated in the present work the temperature dependence of the solubility in the investigated temperature interval is more complex. The solubility data over the temperature range 278 – 318 K was found to be satisfactorily described by Eqn. 1, which has been shown to provide good accuracy and robustness [6]. For ethyl acetate, a simpler function was used (linear with respect to 1/T) by setting two parameters equal to zero. \( x_{eq} \) denotes the mole fraction solubility and \( T \) the temperature in Kelvin. Coefficients of Eqn. 1 are given in Table 3.

\[
\ln x_{eq} = \frac{A}{T^2} + \frac{B}{T} + C + D \ln T
\]

### Table 3. Coefficients of Eqn. 1 for fenoxycarb in various solvents, with associated goodness of fit.

<table>
<thead>
<tr>
<th></th>
<th>Methanol</th>
<th>Ethanol</th>
<th>Isopropanol</th>
<th>Ethyl Acetate</th>
<th>Toluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 10^4 \times A )</td>
<td>2.3177</td>
<td>3.0214</td>
<td>4.0647</td>
<td>-</td>
<td>0.1574</td>
</tr>
<tr>
<td>( 10^4 \times B )</td>
<td>-3.1894</td>
<td>-4.0909</td>
<td>-5.4834</td>
<td>-0.0032314</td>
<td>-0.2255</td>
</tr>
<tr>
<td>( 10^4 \times C )</td>
<td>3.9131</td>
<td>4.9556</td>
<td>6.6247</td>
<td>0.00098976</td>
<td>0.2791</td>
</tr>
<tr>
<td>( 10^1 \times D )</td>
<td>-5.4483</td>
<td>-6.8864</td>
<td>-9.2022</td>
<td>-</td>
<td>-0.3883</td>
</tr>
<tr>
<td>( \chi^2 )</td>
<td>0.00566</td>
<td>0.00242</td>
<td>0.00738</td>
<td>0.00005</td>
<td>0.00004</td>
</tr>
</tbody>
</table>
The mole fraction solubility decreases in the order: ethyl acetate > toluene > methanol > ethanol > isopropanol. Also, although not quantitatively measured in this work, it was observed that fenoxycarb has by far the lowest solubility in water. In the lower temperature range the solubility is clearly lower in all the alcohols. Fenoxycarb has two aromatic rings, and both hydrogen bond donating and accepting functionality. All tested solvents are capable of accepting a hydrogen bond (the π-electron system of toluene’s aromatic ring can act as a weak hydrogen bond acceptor [20]), while ethyl acetate and toluene are incapable of hydrogen bond donation. Hence, neither ethyl acetate nor toluene can hydrogen bond internally, and both are clearly capable of solvating the fenoxycarb molecule. The alcohols have higher cohesive energy and lower capability of solvating the aromatic rings.

3.2 Thermodynamics of the Solid Phase

Choosing the same reference state for the activity of the pure solid as for the solute in solution, viz. the pure compound as a supercooled melt at the same temperature, we have:

\[ a = a_{eq} = x_{eq} \gamma_{eq} \]  

(2)

where \( a \) is the activity of solid fenoxycarb, being equal to the activity of the solute in the saturated solution, \( a_{eq} \), sometimes called the ideal solubility, and \( \gamma_{eq} \) is the activity coefficient, defined within a Raoult’s law framework. The solid-state activity is directly related to the Gibbs free energy of fusion, according to:

\[ \ln a = -\frac{\Delta G_f}{RT} = \frac{\Delta S_f}{R} - \frac{\Delta H_f}{RT} \]  

(3)

If calorimetric data is available, values of the enthalpy and entropy of fusion at a given temperature can be obtained by integration from the melting point \( T_m \):
\[
\ln a = \frac{\Delta H_f(T_m)}{R} \left( \frac{1}{T_m} - \frac{1}{T} \right) + \frac{1}{R} \int_{T_m}^{T} \frac{\Delta C_p}{T} dT - \frac{1}{RT} \int_{T_m}^{T} \Delta C_p dT
\]

where \( \Delta H_f(T_m) \) is the enthalpy change upon melting, and \( \Delta C_p \) is the heat capacity difference between the supercooled pure melt of the solute (used as reference state in the definition of the activity coefficient) and the solid. The melting temperature and the melting enthalpy of fenoxycarb are 326.31 K and 26.98 kJ/mol, respectively [14]. The heat capacity difference has been determined from the heat capacity of the solid and the melt [14] by linear extrapolation of the latter to the supercooled region, Figure 3.

In the temperature interval 270 K – 330 K, the heat capacity difference is accurately (\( R^2 = 0.998 \)) described by a linear equation:

\[
\Delta C_p = q + r(T_m - T)
\]

resulting in \( q = 106.5 \) J/(mol·K) and \( r = 0.0424 \) J/(mol·K²). Insertion of Eqn. 5 into Eqn. 4 and integrating results in:

\[
\ln a = \frac{\Delta H_f(T_m)}{R} \left( \frac{1}{T_m} - \frac{1}{T} \right) - \frac{q}{R} \left( \ln \frac{T_m}{T} - \ln T_m - 1 \right) - \frac{r}{R} \left( T_m \ln \frac{T_m}{T} - \frac{T_m^2}{2T} + \frac{T}{2} \right)
\]

**Figure 3.** Heat capacity of the solid (blue), melt (red) with symbols showing experimental data points [14], dashed lines showing linear extrapolations, and the difference between melt and solid shown in green.

and the Gibbs free energy, enthalpy and entropy of fusion can be calculated by:
\[ \Delta G_f(T) = \Delta H_f(T_m) \left[ 1 - \frac{T}{T_m} \right] + q \left[ T \ln \left( \frac{T_m}{T} \right) - T_m + T \right] \] (7)

\[ + r \left[ T_m T \ln \left( \frac{T_m}{T} \right) - \frac{T_m^2}{2} + \frac{T^2}{2} \right] \]

\[ \Delta H_f(T) = \Delta H_f(T_m) + q(T - T_m) - \frac{r}{2} (T - T_m)^2 \] (8)

\[ \Delta S_f(T) = \frac{\Delta H_f(T_m)}{T_m} + q \ln \left( \frac{T}{T_m} \right) + r \left[ T_m \ln \left( \frac{T}{T_m} \right) - T + T_m \right] \] (9)

Figure 4 shows the Gibbs free energy, enthalpy and entropy of fusion versus temperature. Notably, the Gibbs free energy of fusion is a reasonably small difference between fairly large enthalpic and entropic contributions (~20% at 273 K, decreasing to zero at the melting point). In engineering literature the heat capacity terms are often neglected in calculation of the activity of the solid phase. For comparison, Figure 4 also shows the corresponding curves using the approximation \( \Delta C_P = 0 \), i.e. the enthalpy and entropy of fusion are independent of temperature, leaving only the first term on the right-hand side in Eqn. 6. Notably, this approximation, although generally poor at temperatures far below the melting temperature [21] in this instance leads to only a small error in \( \Delta G_f \). However, it is clear from Figure 4 that this is due to the influence of temperature on the entropy of fusion and on the enthalpy of fusion compensating each other.
Figure 4. $\Delta G_f$ (solid lines), $\Delta H_f$ (dashed lines) and $T\Delta S_f$ (dotted lines) calculated using $\Delta C_p = q + r(T_m - T)$ (thick dark blue lines) and $\Delta C_p = 0$ (thin red lines).

3.3 Solubility Temperature Dependence

The temperature dependence of the solubility yields the so-called van’t Hoff or apparent enthalpy of solution, $\Delta H_{\text{Soln}}^{\text{vH}}$:

$$\left( \frac{\partial \ln x}{\partial T} \right)_{eq} = \frac{\Delta H_{\text{Soln}}^{\text{vH}}}{RT^2}$$

(10)

where $R$ is the universal gas constant and $\Delta H_{\text{Soln}}^{\text{vH}}$ at a given temperature is equal to the slope in a van’t Hoff plot multiplied by $-R$. If $\Delta H_{\text{Soln}}^{\text{vH}}$ is constant, integration of Eqn. 10 yields:

$$\ln x = -\frac{\Delta H_{\text{Soln}}^{\text{vH}}}{RT} + \text{const}$$

(11)

Figure 5 shows the solubility data in a van’t Hoff plot. While the curves for ethyl acetate and toluene are very linear, the alcohol curves are strongly non-linear.

Figure 5. van’t Hoff plot of fenoxycarb solubilities in five organic solvents together with regression lines. Black solid line represents the calculated ideal solubility (Eqn. 6).

In most reported solubility data, a van’t Hoff plot is presented as a straight or almost-straight line, and it is not uncommon to find implicit or explicit statements that a van’t Hoff plot should yield a straight
line, i.e. that the van’t Hoff enthalpy of solution is independent of temperature [22]. However, it can be shown [6] that the full thermodynamic interpretation of the van’t Hoff enthalpy of solution is given by:

$$\Delta H_{\text{So,H}} = \Delta H_f(T_m) + \int_T^{T_m} \Delta C_p dT - RT^2 \left( \frac{\partial \ln \gamma}{\partial T} \right)_{eq}$$  \hspace{1cm} (12)

The first two terms on the right-hand side in Eqn. 12 together represent the enthalpy of fusion at $T$, while the third term contains the temperature derivative of the activity coefficient at equilibrium, $\gamma_{eq}$, in a saturated solution defined within a Raoult’s law framework. It is to be noted that this term is not equal to the enthalpy of mixing, which explains why the van’t Hoff enthalpy of solution differs from the thermodynamic enthalpy of solution [23]. It follows from Eqn. 12 that non-linearity of the van’t Hoff curve can occur because the heat capacity term cannot be neglected, and/or because of the temperature dependence of the activity coefficient. The temperature derivative of the activity coefficient includes the effect of the strongly increasing concentration of the saturated solution with increasing temperature. The behaviour shown in Figure 5 agrees with that predicted by Nordström and Rasmuson [6]. For positive deviations from Raoult’s law significant non-linearity may occur, leading to van’t Hoff plots quite similar to those experimentally observed in the present work. It has also been shown [6] that all solubility curves should converge to the melting temperature/enthalpy of fusion at increasing temperature, which again is observed in our data.

In Figure 6, the van’t Hoff enthalpy of solution is shown together with its component terms (Eqn. 12), as a function of temperature for the five organic solvents. For the sake of this analysis, Eqn. 13, a three-parameter equation obtained from a 3rd order polynomial with respect to $1/T$, has been fitted to the experimental solubility data. With decreasing $T_m-T$, Eqn. 13 exhibits the appropriate limiting behaviour as given by Eqn. 14 a-b, and the fit is only marginally worse overall than that obtained for Eqn. 1. However, as $T$ approaches the lower limit of experimental data, the model starts to deviate in its slope from the experimental data, most clearly seen for ethanol and isopropanol. For this reason, the lower limit of the temperature range in Figure 6 (and in Figure 7 and 8) is 280 K.
\[
\ln x_{eq} = \frac{\Delta H_f(T_m)}{R} \left( \frac{1}{T_m} - \frac{1}{T} \right) + E \left( \frac{1}{T^3} + \frac{2}{T_m^3} - \frac{3}{TT_m^2} \right) + F \left( \frac{1}{T^2} + \frac{1}{T_m^2} - \frac{2}{TT_m} \right)
\]

\[
+ G \left( \ln \frac{T}{T_m} + \frac{T_m}{T} - 1 \right)
\]

\[
\ln x_{eq} = 0 \quad \text{at} \quad T = T_m
\] (13)

\[
\Delta H_{S,ln}^{\text{MH}} = RT^2 \left( \frac{\partial \ln x}{\partial T} \right)_{eq} = \Delta H_f \quad \text{at} \quad T = T_m
\] (14 a)

\[
\Delta H_{S,ln}^{\text{MH}} = RT^2 \left( \frac{\partial \ln x}{\partial T} \right)_{eq} = \Delta H_f \quad \text{at} \quad T = T_m
\] (14 b)
Figure 6. The van’t Hoff enthalpy of solution and its components (Eqn. 12) plotted against temperature for five organic solvents.

It can be seen in Figure 6 that the heat capacity term (i.e. the difference between the red and the green curve) has a relatively weak influence on the van’t Hoff enthalpy of solution, and that it is chiefly the third term in Eqn. 12, the enthalpy change related to dissolving the solute into the solvent, that governs the shape of the van’t Hoff curves, in particular for the alcohols.

The van’t Hoff plot in ethyl acetate forms a straight line (R^2 value of the linear fit is 0.9999) reaching ln x = 1 at the melting point of 326.31 K. The resulting constant van’t Hoff enthalpy of solution in ethyl acetate is essentially identical to the reported enthalpy of fusion at the melting point, 26.98
kJ/mol [14]. Accordingly, the ethyl acetate solution could easily have been mistaken for a perfect ideal solution. However, Figure 6 shows that the heat capacity term is far from negligible but is very well compensated for by the activity coefficient derivative term in ethyl acetate. In toluene, the van’t Hoff enthalpy of solution becomes somewhat higher as the activity coefficient term is larger (i.e. the temperature derivative is more negative). In the alcohols, the activity coefficient term dominates completely, and depends significantly on temperature.

3.4 Solution Activity Coefficients

Inserting the calculated solid-state activity according to Eqn. 6 together with solubility described using Eqn. 13 into Eqn. 2 allows us to estimate the activity coefficient as a function of temperature in the different solvents, Figure 7. In ethyl acetate the maximum value of the activity coefficient within the experimental temperature range is 1.17 and in toluene it is 1.71, in both cases at 278 K. In methanol and ethanol the values are clearly larger and in isopropanol the activity coefficient ranges up to about 18 in the temperature range investigated. All solutions show positive deviation from Raoult’s law and the activity coefficients gradually approach unity with increasing temperature. Activity coefficients close to unity suggest that solute-solute, solute-solvent and solvent-solvent interactions are roughly equal (ideality), while coefficients greater than unity imply solute-solvent interactions significantly weaker than either solvent–solvent interactions and/or solute-solute interactions. Thus it is evident that the alcohol molecules interact more strongly with each other than with fenoxycarb molecules while all intermolecular interactions in fenoxycarb solutions of ethyl acetate and toluene are fairly similar in strength. This is probably owing to the fact that alcohols are both hydrogen donating and accepting while ethyl acetate and toluene are hydrogen bond accepting only.
Figure 7. Activity coefficients in saturated solutions in five organic solvents.

By differentiating Eqn. 13 according to Eqn. 10, and inserting the resulting van't Hoff enthalpy into Eqn. 12, the temperature derivative of the saturated solution activity coefficient in the five solvents is estimated, Figure 8. In general the derivative is negative, i.e. the activity coefficient decreases with increasing temperature, as seen in Figure 7. At temperatures below the range of experimental solubility data some derivatives turn positive; this is an artifact stemming from the use of Eqn. 13 to correlate experimental solubility data. The activity coefficient derivatives range from zero to about -0.12, meaning that in isopropanol at approx. 293 K the activity coefficient changes by about 11 % for every degree Kelvin. On the other hand it might appear surprising that such numerically small values have such a strong impact on the van’t Hoff enthalpy of solution, Figure 6. However, it should be noted that the factor $RT^2$ in Eqn. 12 ranges from 642 to 840 kJ·K/mol over the experimental temperature range, i.e. even very low activity coefficient derivatives will have a sizeable impact, as in the case of ethyl acetate. For the values observed for the alcohols the contribution from the activity coefficient derivative completely dominates the van’t Hoff enthalpy of solution, Figure 6, and the slope of the van’t Hoff curves, Figure 5.
Figure 8. Temperature derivative of the activity coefficient in saturated solutions of five organic solvents.

3.5 Solid Phase Identification

It is conceivable that the strongly non-linear van’t Hoff plots in the alcohols could be a mix of two curves representing two different solid phases (polymorphs or solvate), i.e. a solid phase transformation could occur between 290 and 313 K [4]. During the course of this work, crystals appearing to the naked eye to be quite dissimilar in size and shape have been obtained. Three distinct types of crystals have been found, without any apparent preference, in all solvents and at all temperatures, as shown in Figure 9. Type 1 consists of large (up to 2 mm in the largest dimension), translucent crystals, visibly plate-like in habit, while types 2 and 3 consists of smaller crystals.
**Figure 9.** Side (a) and top (c) views of type 1 and 3 crystals, with close-up of type 1 crystals (b), and type 2 crystals (d). Scale bar represents 0.6 mm.

SEM microscopy revealed all three types to be of the same basic habit (thin platelets) of different sizes and orientation (Figure 10). Type 1 is indeed large platelets (a, b), while crystals of types 2 (c, d) and 3 (e, f) also consist of thin platelets, but tightly packed and with less defined edges.

**Figure 10.** SEM images of crystals appearing as large translucent platelets (a, b), small yellow granules (c, d) and a congealed yellow mass (e, f).
Ex-situ ATR-FTIR analysis of slurries and dried crystals was carried out in all solvents between and inclusive of the temperatures at which solubilities were determined. The same was done in-situ in isopropanol using Raman spectroscopy. However, in no cases were differences in spectra observed after solvent subtraction. This suggests that all crystals were of a single polymorph. Pressure induced polymorph conversion during IR measurement [4] is unlikely as the Raman results, which involve no pressure application, also show no evidence of polymorphism.

Powder XRD analysis resulted in two slightly different diffraction patterns, one for type 1 and the other for both 2 and 3 (Figure 11). There are apparent differences in peak position which occur only between about 18 and 25 °2θ, in which region peaks overlap and the signal does not return to the baseline. The small differences observed in the powder XRD data are typical of the effects of preferred orientation occurring due to slight differences in habits of the same polymorph, which can change peak intensity by up to 100%.[24] Although the habit of both types appears to be identical, it is plausible that the differences in crystal size, aggregation and orientation could lead to preferred orientation effects. Powder XRD spectra of ground crystals of all types (not shown) show no clear difference in preferred orientation.

Figure 11. Powder XRD diffraction patterns observed for fenoxycarb, representative of type 1 (blue) and type 2 (red), with Y axis showing intensity in arbitrary units. Differences in peak position only occur between 18 and 25 ° 2θ, shown magnified in insert.

The samples analysed by powder XRD were also analysed on the same day by solution 1H NMR in deuterated chloroform. In all cases only peaks corresponding to pure fenoxycarb, trace water from
solvents and undeuterated chloroform were detected, i.e. no evidence of solid-state solvation was found. Although the $^1$H NMR water peaks could conceivably hide a water peak from hydrated fenoxycarb, DSC runs up to 353 K show no thermal events characteristic of dehydration.

Analysis of the different solid materials by DSC again yielded two slightly different sets of results (Figure 12). In all cases only a single melting endotherm was observed, with a slightly different onset temperature for the different types, given in Table 4. This difference partly remains after a melting-recrystallization cycle. The slight reduction in melting point for the second cycle in both cases is expected since complete melting and recrystallization in the sample pan should improve heat transfer.

Due partly to the small number of scans (4 and 2, respectively), 95% confidence intervals for the extrapolated onset melting temperatures of types 1 and 2 overlap but all four type 1 values are higher than both type 2 values and closer to the literature value [14]. Values of the enthalpy of fusion for the second cycle were also higher for type 1 than 2/3, but with overlapping confidence intervals. Since the second DSC heat cycle is preceded by complete melting, the minor but significant difference in melting points and enthalpies of fusion between types 1 and 2/3 is most likely caused by a difference in impurity content, rather than differences in crystal size, shape or structure, as melting should remove all solid-state information. As higher impurity content is expected to decrease the melting point [25], type 2/3 is hypothesized to be less pure than type 1.

| Table 4. DSC melting data (mean extrapolated onset temperatures, $T_m$, and associated heats of fusion, $\Delta H_f$, with standard uncertainties, $u$, and 95% confidence intervals) for crystals of types 1 and 2 before and after a melting-recrystallization cycle. |
|---|---|---|---|---|
| | Type 1 | Types 2 & 3 | Lit. data* |
| | $1^{\text{st}}$ cycle | $2^{\text{nd}}$ cycle | $1^{\text{st}}$ cycle | $2^{\text{nd}}$ cycle |
| $T_m$ [K] mean | 326.72 | 326.51 | 325.90 | 325.79 | 326.31 |
| $u$ | 0.134 | 0.066 | 0.090 | 0.165 |
| 95% CI† | 326.29 - 327.14 | 326.30 - 326.71 | 324.76 - 327.04 | 323.69 - 327.88 |
| $\Delta H_f$ [kJ mol$^{-1}$] mean | 28.46 | 28.02 | 26.81 | 26.69 | 26.98 |
| $u$ | 0.250 | 0.156 | 0.129 | 0.105 |
| 95% CI† | 27.67 - 29.26 | 27.52 - 28.52 | 25.17 - 28.45 | 25.36 - 28.02 |

* Xiao-Hong et al. (2005)
† Calculated as mean ± $u \cdot t$, where $t$ is Student’s t-value.
Figure 12. Two DSC plots representative of the two different sets of results observed in the DSC analysis. Blue: type 1; red: type 2/3; solid: first cycle; dotted: second cycle.

Our conclusion is that the observed crystal differences are due only to differences in impurities and crystal size, orientation and agglomeration. Probably, type 1 crystals are formed in the bulk of the solution under low nucleation rates, while the smaller crystals nucleate later, at the air-solution interface at higher nucleation rates, incorporating a larger share of the impurities.

4 Conclusions

Fenoxycarb is highly soluble in ethyl acetate, toluene, and the three lower alcohols at room temperature. All solutions show positive deviation from Raoult’s law. However, in ethyl acetate and toluene these deviations are fairly weak while in the alcohols they are quite strong reaching a maximum activity coefficient in isopropanol of 18. The heat capacity correction to the enthalpy of fusion of pure fenoxycarb is not negligible at room temperature, but there is significant enthalpy-entropy compensation as the temperature changes. The activity coefficient term in the equation for the van’t Hoff enthalpy of solution is small in ethyl acetate and toluene but has a dominating influence in methanol, ethanol and propanol.

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Bibliography

Highlights

Solubility of fenoxycarb in alcohols presents strongly non-linear van't Hoff plots.

Rigorously calculated ideal solubility vs temperature is presented.

The activity coefficients show positive deviation from Raoult’s law.

The activity coefficient derivative dominates the van't Hoff enthalpy of solution.
Graphical abstract

van't Hoff plot of fenoxycarb in organic solvents:

\[ \ln X_{eq} \]

- ideal
- EtOAc
- Toluene
- MeOH
- EtOH
- IPA

fenoxycarb