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Differential Molar Heat Capacities to Test Ideal Solubility Estimations

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Purpose. Calculation of the ideal solubility of a crystalline solute in a liquid solvent requires knowledge of the difference in the molar heat capacity at constant pressure of the solid and the supercooled liquid forms of the solute, $\Delta\overline{C}_P$. Since this parameter is not usually known, two assumptions have been used to simplify the expression. The first is that $\Delta\overline{C}_P$ can be considered equal to zero; the alternate assumption is that the molar entropy of fusion, $\Delta\overline{S}_f$, is an estimate of $\Delta\overline{C}_P$. Reports claiming the superiority of one assumption over the other, on the basis of calculations done using experimentally determined parameters, have appeared in the literature. The validity of the assumptions in predicting the ideal solubility of five structurally unrelated compounds of pharmaceutical interest, with melting points in the range 420 to 470K, was evaluated in this study.

Methods. Solid and liquid heat capacities of each compound near its melting point were determined using differential scanning calorimetry. Linear equations describing the heat capacities were extrapolated to the melting point to generate the differential molar heat capacity.

Results. Linear data were obtained for both crystal and liquid heat capacities of sample and test compounds. For each sample, ideal solubility at 298K was calculated and compared to the two estimates generated using literature equations based on the differential molar heat capacity assumptions.

Conclusions. For the compounds studied, $\Delta\overline{C}_P$ was not negligible and was closer to $\Delta\overline{S}_f$ than to zero. However, neither of the two assumptions was valid for accurately estimating the ideal solubility as given by the full equation.

KEY WORDS: differential heat capacity; differential scanning calorimetry; heat capacity; heat capacity assumptions; ideal solutions.

INTRODUCTION

The equation for the ideal solubility of a crystalline solute in a liquid solvent is:

$$\ln X_2 = \frac{-\Delta\overline{H}_f}{R}\left(\frac{T_m - T}{T_m T}\right) + \frac{\Delta\overline{C}_P}{R}\left(\frac{T_m - T}{T}\right) - \frac{\Delta\overline{C}_P}{R}\ln\frac{T_m}{T} \tag{1}$$

where $\Delta\overline{H}_f$ refers to the molar enthalpy of fusion at the melting point of the pure solute, T_m is the absolute melting point, T is the absolute solution temperature, R is the ideal gas constant, and X_2 refers to the mole fraction solubility of the solute in question. The differential molar heat capacity, $\Delta\overline{C}_P$, which is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical supercooled liquid form, both at the solution temperature, is included in this expression to acknowledge the influence of these heat capacity effects on the enthalpy required to dissolve the crystalline material. This equation has been simplified by making one of two assumptions regarding the differential molar heat capacity at constant pressure: (i) $\Delta\overline{C}_P$ is negligible and can be considered zero or (ii) $\Delta\overline{C}_P$ may be approximated by the entropy of fusion, $\Delta\overline{S}_f$. Simplification of this equation in this manner was pursued because $\Delta\overline{C}_P$ is the only parameter in the expression that cannot be readily determined experimentally (1).

An equilibrium constant is related to the change in the molar Gibb's free energy of the process, $\Delta\overline{G}$, by the familiar expression:

$$\Delta\overline{G} = -RT \ln K \tag{2}$$

If K refers to the equilibrium between a solute in an ideal solution and in its crystalline form, both at the temperature T, then equation 2 can be expressed as:

$$\Delta\overline{G}_f = -RT \ln X_2 \tag{3}$$

where $\Delta\overline{G}_f$ is the change in free energy for the melting process. Rearranging gives:

$$\ln X_2 = \frac{-\Delta\overline{G}_f}{RT} \tag{4}$$

Taking the partial derivative of equation 4 with respect to T gives:

$$\left(\frac{\partial \ln X_2}{\partial T}\right)_P = \left(\frac{\partial(-\Delta\overline{G}_f/RT)}{\partial T}\right)_P = \frac{\Delta\overline{H}_f}{RT^2} \tag{5}$$

Allowing for heat capacity effects, equation 5 can be integrated from the temperature of the solution, T, to the melting point, T_m, to give equation 1. If indeed $\Delta\overline{C}_P$ were equal to zero, equation 1 reduces to:

$$\ln X_2 = \frac{-\Delta\overline{H}_f}{R}\left(\frac{T_m - T}{T_m T}\right) \tag{6}$$

and a plot of $\ln X_2$ as a function of 1/T would be a straight line.

Equation 6 has been employed in many reports (2–6). Yalkowsky (7) decided that $\Delta\overline{C}_P$ is relatively close to zero, particularly for compounds that melt at higher temperatures. This would be a premature conclusion since a threshold temperature was not specified and only data for polyaromatic hydrocarbons were considered.

Hildebrand *et al.* (8) observed a linear relationship between $\log X_2$ and $\log T$, and, to support this observation, presented a mathematical argument that can be summarized as follows.

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NOTATION: $\overline{C}_P$, the molar heat capacity at constant pressure; $\Delta\overline{C}_P$, the differential molar heat capacity at constant pressure; $\overline{C}_{P,s}$, the molar heat capacity of the crystal form at the melting point; $\overline{C}_{P,l}$, the molar heat capacity of the liquid form at the melting point; $\Delta\overline{G}_f$, the change in Gibb's free energy for the melting process; $\Delta\overline{H}_f$, the molar enthalpy of fusion of the pure solute at its melting point; ΔH_{p+l}, the total differential heat provided to the empty sample pan and lid; ΔH_{p+l+s}, the heat introduced into the unit consisting of the pan, lid, and sample; ΔH_s, the enthalpy requirement of the sample over a ten degree range; R, the ideal gas constant; $\Delta\overline{S}_f$, the molar entropy of fusion; T, the solution temperature in degrees Kelvin; T_m, the melting point in degrees Kelvin; X, the mole fraction solubility of the solute in the ideal solution.

Rewriting equation 5 as the first partial derivative with respect to lnT:

$$\left(\frac{\partial \ln X_2}{\partial \ln T}\right)_P = \frac{\Delta\bar{H}_f}{RT} \tag{7}$$

and taking the second derivative gives:

$$\left(\frac{\partial^2 \ln X_2}{(\partial \ln T)^2}\right)_P = T\left[\frac{\partial}{\partial T}\left(\frac{\Delta\bar{H}_f}{RT}\right)\right]_P = \frac{\Delta\bar{C}_P}{R} - \frac{\Delta\bar{H}_f}{RT} \tag{8}$$

At the melting point, $\Delta\bar{G}_f = 0$ and $\Delta\bar{H}_f = T\Delta\bar{S}_f$. If $\Delta\bar{C}_P$ can be approximated by $\Delta\bar{S}_f$, then (i) the second derivative given in equation 8 is zero at the melting point, (ii) the first derivative would be a constant with respect to lnT, and (iii) $\ln X_2$ would be a linear function of lnT. Therefore, the empirical observation that $\log X_2$ is a linear function of logT indicates that setting $\Delta\bar{C}_P$ equal to $\Delta\bar{S}_f$ can be considered as valid as the practice of setting $\Delta\bar{C}_P$ equal to zero. If $\Delta\bar{C}_P$ can be approximated by $\Delta\bar{S}_f$, then equation 1 reduces to:

$$\ln X_2 = -\frac{\Delta\bar{H}_f}{RT_m}\ln\frac{T_m}{T} \tag{9}$$

Equation 9 has been used by Mauger *et al.* (9), Martin *et al.* (10), Richardson *et al.* (11), and Subrahmanyam *et al.* (12), and has been shown by Grant *et al.* (13) to provide a better fit with respect to available experimental solubility data. Neau *et al.* (1) observed that solubilities calculated using equations 6 and 9 are essentially equal when T_m and T are close. Evidence that a higher melting point would more profoundly influence the difference in estimated solubilities was also presented.

Neau and Flynn (14) examined the validity of each of the two assumptions using a homologous series of n-alkyl para-aminobenzoates as test compounds. Although these compounds presented a melting point range restricted to 325 to 386K, the authors concluded that $\Delta\bar{C}_P$ was closer to $\Delta\bar{S}_f$ than to zero. A similar conclusion was drawn by the authors after a comparison of heat capacity and entropy of fusion data compiled from literature data on 41 organic compounds. The noted exceptions to that conclusion were data for benzene and unsubstituted polyaromatic hydrocarbons, where the assumption of a negligible differential heat capacity holds. The authors suggested that the rigidity of these molecules limits both the entropy of fusion and the change in heat capacity on melting.

Using a subset from this data compilation, Mishra and Yalkowsky (15) statistically evaluated the validity of the two assumptions. The authors concluded that ideal solubility calculated using equation 6, under the assumption that $\Delta\bar{C}_P = 0$, gives a lower numerical difference from the solubility calculated using equation 1 than does the solubility calculated using equation 9 which was derived using the assumption that $\Delta\bar{C}_P = \Delta\bar{S}_f$. In addition, the authors stated that equation 6 was simpler to use, and that a presumed theoretical superiority should not be the basis for choosing an assumption. The data selected from the compilation, however, was biased in favor of polyaromatic hydrocarbons and was limited to 16 compounds. Furthermore, it should be noted that equations 9 and 6 are both easy to employ since even hand-held calculators are capable of logarithmic transformations. The choice between them should not be based solely on the simplest resulting equation.

The aim of this work is twofold: (i) to test the hypothesis that organic compounds that melt at higher temperatures possess a negligible differential heat capacity and (ii) to examine the validity of the two assumptions using compounds that melt between 420 and 470K. This temperature range was chosen because these melting points can result in differences of 20 to 27 percent in calculated $\ln X_2$ for solutions at 298K when using equations 6 and 9.

MATERIALS AND METHODS

Materials

Sapphire (α-corundum; aluminum oxide) (Perkin Elmer Corp., Norwalk, CA) was used as the heat capacity standard in this study. Indium (Perkin Elmer) was the standard for temperature and enthalpy of fusion. The performance of the calorimeter was evaluated using two test compounds, anthracene (Fisher Scientific, Fair Lawn, NJ), and biphenyl (Eastman Organic Chemicals, Rochester, NY). The compounds included in this study were anisic acid (Eastman Organic Chemicals), acetaminophen (Ruger Chemical Co., Irvington, NJ), diethylstilbestrol (Sigma Chemical Company., St. Louis, MO), mannitol (Difco Labs, Detroit, MI), and naproxen (Sigma). These sample compounds were available in the crystalline state and had melting points between 420 and 470K. Their chemical structures are presented in Figure 1. The stability of the samples in the temperature range studied was confirmed by observing no visual indications of decomposition on heating, no anomalous thermal behavior in the DSC thermograms when the samples were heated across the desired temperature range, and the linear relationships between the heat capacities and temperature. The test and sample compounds were all determined to be of greater than 99% purity by calorimetric purity estimation.

Methods

The calorimetric measurements were accomplished using a Perkin Elmer DSC-4 differential scanning calorimeter, and the data was recorded and analyzed using Laboratory Microsystems Thermal Analysis Software Version 9 (TAV9), loaded on an

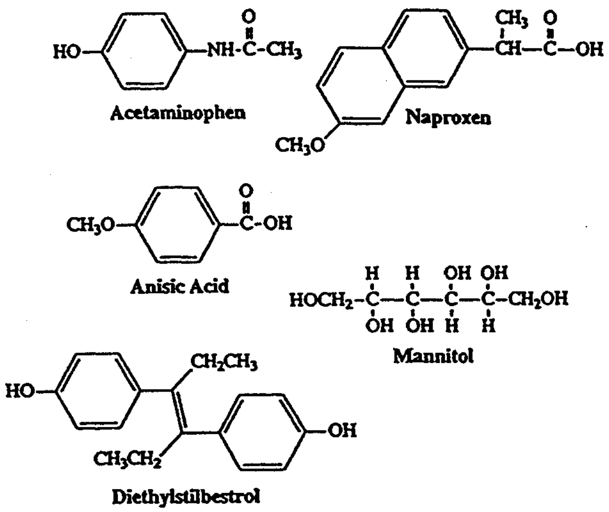

Fig. 1. Chemical structures of sample compounds.

IBM PS/2 model 50Z computer. A continuous flow of nitrogen gas was maintained through the sample and reference holders of the DSC.

For melting point, enthalpy of fusion and purity determinations, a sample of between 2 and 7 mg was accurately weighed in an aluminum pan on a Mettler AT261 balance. An aluminum lid was then crimped on the pan. An empty pan and lid served as the reference. The reference and each sample were heated at 1 degree per minute over a 10 degree range centered at the melting point. Melting points were determined from the onset of melting. Enthalpies of fusion were determined from the area under the melting endotherm. Both melting point and enthalpy of fusion were corrected using indium results from the same day. Purities were evaluated by using software from Laboratory MicroSystems, Inc. (Troy, NY) which employed partial areas under the melting endotherm as designated by the user.

For the heat capacity determinations, an empty pan and lid were placed in the sample holder and an empty pan served as the reference. The protocol was adapted from that described by O'Neill (16). The sample and reference were initially equilibrated isothermally, heated at 1 degree per minute for 10 degrees, and then equilibrated isothermally at the higher temperature for two minutes. The DSC-4 could be programmed for three of these heating-isothermal runs, so a range of 30 degrees could be covered during one scan.

The heat capacity of the sapphire standard was measured over the entire range of 355 to 535K. Sample solid heat capacities were measured from about 70 degrees below to 10 degrees below the respective melting point. Heat capacity measurements closer to the melting point may present anomalies due to premelting behavior. Sample liquid heat capacities were measured up to about 70 degrees above the melting point.

For each ten minute heating period, the thermogram presented a trapezoidal peak which represents the differential flow of heat, dH/dt, to the sample side that was necessary to keep the sample and reference side at essentially the same temperature at every time point during the run. Integration of this peak area with respect to time, as provided by the software, gave the total differential heat provided to the empty sample pan and lid, ΔH_{p+l}.

Once the temperature range of interest was covered, the sample pan and lid were cooled to room temperature and an accurately weighed, 2 to 10 mg, powdered sample was introduced into the pan, and the lid was crimped on. This unit was then placed in the sample side of the calorimeter, and runs similar to the ones described for the empty pan and lid were carried out. Thus, the heat introduced into the unit consisting of the pan, lid, and sample, ΔH_{p+l+s}, was determined. The difference between ΔH_{p+l+s} and the corresponding ΔH_{p+l} for a given temperature range equals the enthalpy requirement of the powdered sample, ΔH_s. This is related to the molar heat capacity by the expression:

$$\Delta H_s = \frac{m\overline{C}_P\,dT}{M} \tag{10}$$

where m is the mass of the sample in grams, M is the molecular weight of the sample compound, and dT is the temperature range of the run (10 degrees in this study). $\overline{C}_P$ is the molar heat capacity at constant pressure, and the value of $\overline{C}_P$ obtained for the ten degree range was assigned to the mean temperature. Thus, for example, the heat capacity determined for a run from 355 to 365K was assigned to 360K.

Heat capacities for sapphire were carried out routinely. The observed heat capacities for samples and test compounds were corrected using any deviations of the experimental heat capacity for sapphire from the literature values (17) at the corresponding temperature. The correction was accomplished using the following formula:

$$(\text{corrected } \overline{C}_P)_T = (\text{experimental } \overline{C}_P)_T \left(\frac{\text{literature sapphire } \overline{C}_P}{\text{experimental sapphire } \overline{C}_P}\right)_T \tag{11}$$

On those occasions when the observed sapphire values deviated by more than 5% from their literature values, the sample values were discarded.

To test the ability of the calorimeter to accurately measure heat capacities of a crystalline organic compound, anthracene heat capacities were determined in the temperature range over which solid sample heat capacities were measured. Biphenyl was used as the corresponding liquid test compound. The experimental heat capacities of these two test compounds were compared to literature values (18,19). The literature values were obtained using adiabatic calorimetry, which is a more accurate, albeit a slower and more tedious, method for the measurement of heat capacities. Heat capacities for sample and test compounds were determined at least in triplicate. Statistical analysis of the data was performed and, whenever necessary, individual heat capacities were removed from consideration if they were more than two standard deviations away from the mean heat capacity for that temperature range.

RESULTS AND DISCUSSION

The experimental physicochemical properties of the test and sample compounds are presented in Table 1. The heat capacity results for anthracene and biphenyl compared favorably with the literature values. On the average, anthracene heat capacities deviated from literature values by 2.4%, and biphenyl heat capacities by 1.4%. It is expected that sample heat capacities reflect the same accuracy. Sample heat capacities are presented in Tables 2 and 3. In two cases, noted in the footnote for Table 3, a mean liquid heat capacity value was considered a statistical outlier, and was not included in calculating the linear relation, if it was outside the range defined by the heat capacity, calculated using the linear relation derived without that value included, plus or minus two times the standard error of the estimate of the regression line.

If considering a narrow enough temperature range, heat capacities at constant pressure can be expressed as a linear function of temperature (16,20). Although $\Delta\overline{C}_P$ actually refers to the difference between the heat capacity of a hypothetical supercooled liquid form and that of the crystalline form of the solute at the solution temperature, this is a parameter that cannot be measured. It is customary to approximate it using the differential heat capacity at the melting point, that is, the difference between the heat capacity of the liquid and solid forms of the compound at its melting point. To determine $\Delta\overline{C}_P$, linear relations between $\overline{C}_P$ and temperature were generated for solid and for liquid heat capacities (see Table 4) and $\overline{C}_P$ was extrapolated to the melting point to determine $\overline{C}_{P,s}$ and $\overline{C}_{P,l}$ respectively

Table 1. Physicochemical Properties of Sample and Test Compounds

Compound	Acetaminophen	Anisic acid	Anthracene	Biphenyl	Diethylstilbestrol	Mannitol	Naproxen
Purity (%)[a]	>99.9	>99.9	99.9	99.9	99.8	>99.9	>99.9
Melting Onset (K)	441.7	455.4	487.8	342.7	441.8	438.7	428.5
Molar Enthalpy of Fusion[b]	27.0 (0.5)	27.8 (0.8)	26.5 (1.3)	18.0 (0.5)	28.8 (1.2)	50.6 (0.7)	31.5 (2.1)
Molar Entropy of Fusion[c]	60.9	61.1	54.3	52.5	65.1	115.3	73.5

[a] The reported value for the purity and melting point is the mean of three measurements.

[b] Enthalpy is reported in kJ/mole. The enthalpy of fusion values are each the mean (r.s.d, %) of triplicate measurements.

[c] Entropy is reported in J/(mole·K).

Table 2. Crystal Heat Capacities

Absolute Temperature	Acetaminophen	Anisic Acid	Diethylstilbestrol	Mannitol	Naproxen
370	218.2 (2.9)	—	—	299.8 (1.7)	336.8 (0.5)
380	223.7 (1.7)	—	478.8 (3.6)	307.0 (2.4)	351.7 (4.4)
390	231.9 (1.8)	243.0 (3.4)	494.2 (3.5)	318.3 (1.6)	360.7 (2.7)
400	239.0 (2.5)	249.2 (0.3)	514.6 (3.7)	329.8 (2.2)	370.9 (4.7)
410	245.6 (2.8)	257.9 (1.7)	536.4 (3.0)	342.6 (3.4)	387.2 (3.9)
420	250.5 (2.7)	265.4 (2.0)	558.7 (4.8)	—	—
430	—	274.3 (1.7)	—	—	—

Note: Values reported in J/(mole·K) are the mean (r.s.d., %) for a minimum of three measurements.

Table 3. Liquid Heat Capacities

Absolute Temperature	Acetaminophen	Anisic Acid	Diethylstilbestrol	Mannitol	Naproxen
450	—	—	—	—	524.4 (1.5)
460	—	—	654.0 (3.2)	540.0 (1.8)	526.4 (1.8)
470	371.9 (2.9)	—	658.4 (1.9)	541.6 (1.5)	530.5 (2.1)
480	373.4 (0.5)	384.1 (0.6)	663.4 (3.2)	543.8 (1.4)	534.5 (1.6)
490	376.5 (2.5)	387.3 (1.2)	668.4 (2.9)	545.7 (1.0)	538.4 (2.0)
500	378.4 (1.7)	386.7 (2.3)[a]	660.5 (3.5)[a]	546.5 (1.7)	540.5 (1.9)
510	379.9 (1.7)	392.8 (2.7)	678.7 (3.3)	549.5 (1.6)	—
520	—	398.6 (2.9)	—	—	—
530	—	401.4 (0.9)	—	—	—

Note: Values reported in J/(mole·K) are the mean (r.s.d., %) for a minimum of three measurements.

[a] These values proved to be outliers, and were not included in the linear regression analysis.

Table 4. Heat Capacities and Calculated Ideal Solubilities

Compound	Acetaminophen	Anisic Acid	Diethylstilbestrol	Mannitol	Naproxen
Liquid Heat Capacity[a]	273.2 + 0.2099 T/K $r^2 = 0.987$	216.4 + 0.3487 T/K $r^2 = 0.986$	424.7 + 0.4977 T/K $r^2 = 0.998$	455.3 + 0.1840 T/K $r^2 = 0.985$	369.0 + 0.3440 T/K $r^2 = 0.989$
Crystal Heat Capacity	−29.34 + 0.6688 T/K $r^2 = 0.995$	−65.24 + 0.7883 T/K $r^2 = 0.997$	−291.2 + 2.019 T/K $r^2 = 0.999$	−103.3 + 1.084 T/K $r^2 = 0.991$	−106.8 + 1.201 T/K $r^2 = 0.989$
Differential Heat Capacity[b]	99.8 ± 2.8	81.7 ± 3.5	43.6 ± 5.6	163.7 ± 4.7	108.6 ± 5.9
Molar Entropy of Fusion[c]	60.9	61.1	65.1	115.3	73.5
Ideal Solubility (eq. 1)[d]	−2.464	−2.854	−3.307	−4.858	−2.891
Ideal Solubility (eq. 6)	−3.525	−3.874	−3.776	−6.534	−3.863
Ideal Solubility (eq. 9)	−2.878	−3.111	−3.078	−5.354	−3.205

[a] Heat capacities are reported in J/(mole·K) units.

[b] The differential heat capacity, calculated as the difference between the extrapolated values at the melting point, is reported in J/(mole·K). Standard deviations were calculated using the standard error of the estimate for the respective regression lines.

[c] Entropies of fusion are reported in J/(mole·K) units.

[d] These values are the calculated ideal solubilities, as ln X_2, at 298.2 K. Eq. 1 is the full solubility equation. Eq. 6 is based on the assumption that $\Delta\overline{C}_P = 0$. Eq. 9 assumes that $\Delta\overline{C}_P$ can be estimated by the entropy of fusion.

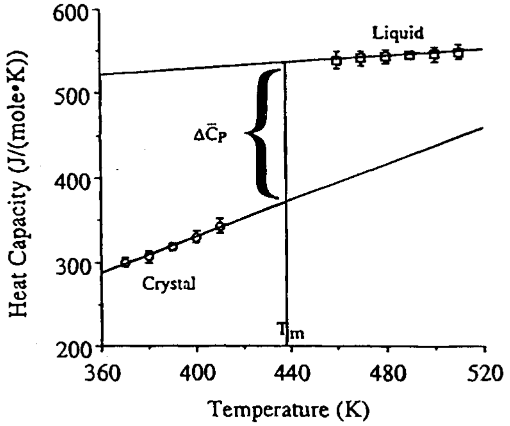

Fig. 2. Extrapolated linear heat capacity relationships for mannitol and the presentation of the differential molar heat capacity.

(14). The differential heat capacity was then obtained from the difference:

$$\Delta\bar{C}_P = \bar{C}_{P,l} - \bar{C}_{P,s} \tag{12}$$

An example of extrapolated heat capacities and a presentation of $\Delta\bar{C}_P$ are offered in Figure 2. The values for the differential heat capacity at the melting point are presented, along with the entropy of fusion, in Table 4. Note that $\Delta\bar{C}_P$ in each case is not negligible and indeed is closer to the entropy of fusion than to zero. Therefore, the assumption by Yalkowsky that differential heat capacities are negligible for high melting compounds does not hold.

The ideal solubility, $\ln X_2$, for each sample compound was calculated using equations 1, 6, and 9 for comparison purposes, and the results are presented in Table 4. Heat capacity terms in equation 1 result in at least a 59% increase and as high as a 189% increase in the ideal mole fraction solubility, when compared to the solubility predicted using equation 6. Therefore, the contribution of heat capacity to the predicted ideal solubility is not negligible in these cases. The mole fraction solubility calculated using equation 1 is 1.32 (±0.32) times that predicted by equation 9, whereas it is 3.05 (±1.38) times that predicted using equation 6. Thus, in this study, acknowledging that the differential heat capacity is not negligible, and approximating it with the entropy of fusion, led to a more reasonable estimate of the ideal solubility. It should be noted, however, that neither equation 6 nor 9 provides an accurate estimate of the ideal solubility.

CONCLUSIONS

Since neither equation based on an assumption regarding the differential molar heat capacity yielded a close approximation of the ideal mole fraction solubility, the heat capacity terms should be included for accurate thermodynamic predictions of ideal mole fraction solubilities. The hypothesis that the differential molar heat capacity is negligible for high melting compounds was proved false in these five cases. For the data presented here, the assumption that the differential heat capacity is not negligible but instead could be estimated by the entropy of fusion provided a more reasonable estimate of the ideal solubility. Since this study is limited to five compounds, the influence of the differential molar heat capacity of high melting organic compounds on solubility warrants further study.

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