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Report

Solid and Liquid Heat Capacities of *n*-Alkyl Para-aminobenzoates Near the Melting Point

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The expression that relates the ideal mole fraction solubility of a crystalline compound to physicochemical properties of the compound includes a term involving the difference in the heat capacities of the solid and liquid forms of the solute, ΔC_P. There are two alternate conventions which are employed to eliminate this term. The first assumes that the term involving ΔC_P, or ΔC_P itself, is zero. The alternate assumption assigns the value of the entropy of fusion to the differential heat capacity. The relative validity of these two assumptions was evaluated using the straight-chain alkyl para-aminobenzoates as test compounds. The heat capacities of the solid and liquid forms of each of the para-aminobenzoates, near the respective melting point, were determined by differential scanning calorimetry. The data lead one to conclude that the assumption that the differential heat capacity is not usually negligible and is better approximated by the entropy of fusion.

KEY WORDS: alkyl para-aminobenzoates; differential scanning calorimetry; heat capacity; ideal solutions.

INTRODUCTION

The solubility of a crystalline organic compound, in any solvent, is dependent on those physical properties of the crystal which relate to the energy of disengagement of molecules from the crystal. This critical energy can be expressed in terms of the melting point, T_f; the enthalpy of fusion, ΔH_f; and the difference in heat capacity, at constant pressure and at the experimental temperature, between the liquid and the solid forms of the organic compound, ΔC_P. Using these physicochemical properties, the ideal solubility of a crystalline compound in a solvent, where there is no excess enthalpy or excess entropy of mixing, is given by

$$\ln X_2^i = \frac{-\Delta H_f(T_f - T)}{RTT_f} + \frac{\Delta C_P}{R}\left\{\frac{(T_f - T)}{T} + \ln\frac{T}{T_f}\right\} \qquad (1)$$

where T is the temperature of the solution, R is the gas constant, and X_2^i is the mole fraction of the organic solute forming the solution (1). The only assumption made to reach this equation is that, between the melting point and the temperature of the experiment, a fixed difference exists between the heat capacity of the solid state and that of the liquid state of the solute.

Estimation of the ideal solubility of a compound requires a fair estimate of ΔC_P. The literature contains little data on both the solid and the liquid phase heat capacities of organic compounds and therefore it is rare when there are actual data by which to calculate ΔC_P for a specific compound. Consequently, ΔC_P is usually assigned a value based on one or the other of two conventions. It has been reasoned that, since $(T_f - T)/T$ is approximately equal to $\ln(T_f/T)$, the term involving ΔC_P in Eq. (1) approaches the point of being negligible. The simplifying assumption that is frequently used, then, is that the term involving ΔC_P, or ΔC_P itself, is zero, leading to

$$\ln X_2^i = \frac{-\Delta H_f(T_f - T)}{RTT_f} \qquad (2)$$

According to this equation, a plot of $\ln X_2^i$ versus $1/T$ should be linear.

However, ΔC_P will not normally be zero, nor is the second right-hand term in Eq. (1) always negligible. Hildebrand and others (1) observed that there are advantages to a plot of $\log X_2^i$ versus $\log T$. Therefore, an alternate assumption that ΔC_P can be estimated by the entropy of fusion has been offered. Employing this alternate estimation of ΔC_P simplifies Eq. (1) to

$$\ln X_2^i = \frac{\Delta H_f}{RT_f}\ln\frac{T}{T_f} \qquad (3)$$

In this instance, a plot of $\ln X_2^i$ versus $\ln(T)$ should be linear. Equation (2) has been particularly favored by many workers in the pharmaceutical field (2–7). Equation (3) has been used by Mauger (8) and Martin (9) and has been shown by Hildebrand (1) and Grant (10) and their co-workers to provide a

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better fit with respect to available experimental solubility data.

It would be informative to have actual hard data on ΔC_P at the melting point to evaluate the relative validity of these alternative approximations. It was the aim of this work to gather experimental heat capacity data for the *n*-alkyl para-aminobenzoates so that this evaluation could be made.

MATERIALS AND METHODS

Materials

The solutes studied were all straight-chain esters of para-aminobenzoic acid. The first four members of this series were commercially available. Methyl para-aminobenzoate was obtained from Eastman Kodak or Aldrich. The ethyl and *n*-butyl esters were from Sigma Chemical Company. *n*-Propyl para-aminobenzoate was obtained from ICN Biomedicals, Inc., K&K Labs.

Esters higher than the *n*-butyl ester were synthesized according to a literature method (2). The corresponding para-nitrobenzoate was made by warming and stirring a mixture of the appropriate alcohol (Sigma) and para-nitrobenzoyl chloride (Aldrich), which resulted in HCl gas formation. After several hours of stirring, the absence of gas formation indicated the reaction was complete. The mixture was dissolved in ethyl ether (Mallinckrodt), and the solution was neutralized by a 10% aqueous solution of sodium carbonate (Baker). The ether solution was dried with magnesium sulfate (E M Science) and the ether was evaporated. The crude para-nitrobenzoate was then dissolved in absolute ethanol (U.S. Industrial Chemicals Co.) and the nitro group was reduced by use of a Parr hydrogenator and hydrogen gas with 5% palladium on charcoal (MCB Manufacturing Chemicals, Inc.) as a catalyst. The charcoal was filtered off and the ethanol evaporated. The synthesized para-aminobenzoates and those commercially available esters that were impure were recrystallized from *n*-hexane or *n*-heptane until greater than 98% pure as confirmed by calorimetric purity (11).

Differential Scanning Calorimetry

Enthalpy of Fusion and Melting Point. The melting points and enthalpies of fusion of the *n*-alkyl para-aminobenzoates were determined by differential scanning calorimetry. A Perkin-Elmer DSC 2C was calibrated with an indium standard. Accurately weighed samples (1–10 mg) were placed in aluminum crucibles on which an aluminum lid was crimped. An empty aluminum crucible and lid served as the reference. Samples were heated at 1 deg/min for melting point determinations and at 1–10 deg/min for enthalpy of fusion determinations.

Heat Capacities. The heat capacity values near the melting point for both the solid and the liquid forms of the compounds were determined by a modified literature method (12) using the differential scanning calorimeter. An empty aluminum pan and lid were placed in the sample side and an empty pan and lid served as the reference. The sample and reference were equilibrated isothermally and then heated at a constant rate of 10 or 20 deg/min for a 10-degree range. This high heating rate was necessary to generate a measurable pen deflection on the strip chart recorder when the sample size was kept low (1–6 mg). The isothermal equilibration gave a smooth baseline. When heat is applied, there is a deviation from the isothermal baseline, which indicates that heating the sample side required an amount of energy different from that required by the reference side. After the heating phase was completed, the calorimeter was again allowed to equilibrate isothermally at the higher temperature and the baseline was reestablished. This process of isothermal equilibration and heating was repeated to cover a temperature range that included 30 deg or more for the solid form and 40 deg for the liquid form of the sample of interest. The heat capacities of the solid form were determined only up to 10 deg below the melting point to avoid, insofar as possible, any enthalpy contributions associated with premelting phenomena.

After the temperature range of interest was covered, the sample pan was cooled to room temperature and a sample of known mass was introduced into the pan and the lid was sealed. The strip chart recorder was set back to the beginning of the empty pan endotherms and the process of equilibration and heating was repeated with the sample in place over the same temperature range covered when the pan was empty. The recorder pen was aligned with the baselines generated by the empty pan and lid such that the sample and pan isothermal baselines coincided with the empty pan isothermal baselines. The results of this procedure are illustrated in Fig. 1.

This process was repeated for standard compounds, aluminum oxide (Aldrich, 99% pure), and diphenyl ether (Aldrich, 99% pure). Diphenyl ether is a liquid over the temperature range for which it was the standard compound. However, the temperature range of interest for certain of the esters was below the melting point (300 K) of diphenyl ether. The standard chosen for heat capacity measurements should be without transitions over the temperature range for which it is a standard. Consequently, aluminum oxide (α-corundum), a solid, was chosen as a second standard.

There is a difference in the heating phase endotherms due to the additional energy requirement to heat the sample in the sealed pan (Fig. 1). This vertical height difference in mm between the sample and pan endotherm and the empty pan endotherm, y, is proportional to the heat flow rate, dH/dt, to the sample alone:

$$y \alpha \left(\frac{dH}{dt}\right) \tag{4}$$

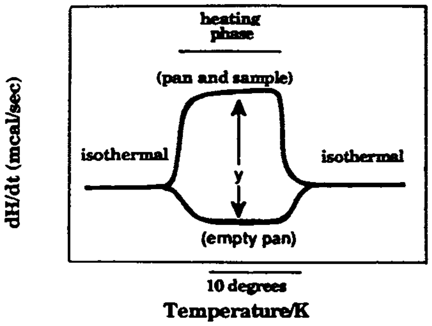

Fig. 1. Endotherms for determination of heat capacity.

The heat flow rate, *dH/dt*, in turn, is directly related to the heat capacity of the sample at that temperature:

$$\left(\frac{dH}{dt}\right) = mC_P \left(\frac{dT}{dt}\right) \qquad (5)$$

where dH/dt is in calories per second, m is the sample mass in grams, C_P is the heat capacity of the sample in calories per gram · degree, and *dT/dt* is the heating rate in degrees per second. This program was repeated so that endotherms and the respective baseline endotherms exist for each sample, as well as the standard, through the temperature range of interest. A comparison could then be made of the vertical height difference between a sample and its empty pan baseline y, and the vertical height difference between a standard and its empty pan baseline, y_{AO}, both at the same temperature and with the vertical heights normalized to the same ordinate scale:

$$\frac{y}{y_{AO}} = \frac{mC_P}{m_{AO}C_{P_{AO}}} \qquad (6)$$

O'Neill (12) described how to calculate sample heat capacities by rearrangement of Eq. (6):

$$C_P = \frac{m_{AO}C_{P_{AO}}\, y}{m y_{AO}} \qquad (7)$$

where C_P is the heat capacity of the sample in calories per gram · degree, m_{AO} is the mass of the aluminum oxide (or diphenyl ether) standard in grams, $C_{P_{AO}}$ is the literature value for the heat capacity of aluminum oxide (or diphenyl ether) in calories per gram · degree, and y_{AO} is the vertical height difference in millimeters between the standard and pan endotherm and its respective empty pan endotherm.

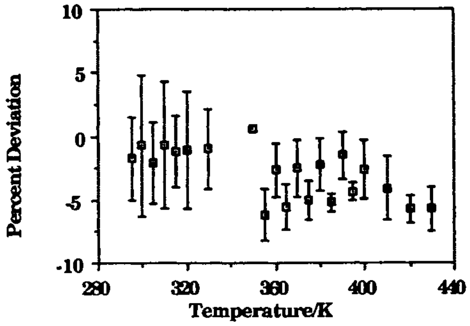

Fig. 2. Deviation of experimental biphenyl heat capacities from literature values. The squares represent the deviation of the mean experimental heat capacity from the literature value. Error bars indicate the extent of deviation corresponding to the standard deviation of the mean.

To test the validity of using a standard that exists in a single physical state to calculate the heat capacities of a sample that has a transition from one physical state to another, a test compound, biphenyl (Aldrich), was studied which has literature values for its heat capacity, both in the solid and in the liquid form (13), and which had a melting point in the same range as the para-aminobenzoates. Biphenyl was included as a sample on each experiment day, and the calculated heat capacities were compared to the literature values. Percentage deviations from the literature values are presented in Fig. 2. On those occasions when the percentage deviation was greater than 10%, the sample data were discarded unless the results could be confirmed when the deviation was less than 5%. By assuming that any deviation was due to human or machine error, this comparison also provided a correction factor at a particular temperature, T, for the sample heat capacities:

$$(\text{corrected } C_P)_T = (\text{calculated } C_P)_T \left(\frac{(\text{literature biphenyl } C_P)}{(\text{calculated biphenyl } C_P)}\right)_T \qquad (8)$$

Liquid heat capacities were corrected using the literature and calculated biphenyl liquid phase heat capacities. Solid heat capacities were corrected using literature and calculated biphenyl solid heat capacities.

Table I. Experimental Solid Heat Capacities, C_p

	Temperature (K)						
	295	300	305	310	315	320	330
Methyl p-aminobenzoate		47.8[a]		49.0		50.4	52.6
		(1.6)[b]		(1.9)		(1.2)	(1.3)
Ethyl p-aminobenzoate		56.5		57.9		60.2	61.5
		(1.9)		(1.6)		(1.7)	(0.9)
n-Propyl p-aminobenzoate		69.9		72.0		74.0	
		(1.1)		(1.7)		(2.5)	
n-Butyl p-aminobenzoate		73.6		76.0		79.2	
		(3.1)		(3.1)		(2.6)	
n-Pentyl p-aminobenzoate	72.7		76.1		79.7		
	(2.3)		(1.0)		(1.3)		
n-Hexyl p-aminobenzoate	80.5		84.6		88.0		
	(2.9)		(2.8)		(1.2)		
n-Nonyl p-aminobenzoate		101		106		110	
		(4)		(3)		(4)	

[a] Mean heat capacity in cal/(mol * deg).

[b] Standard deviation in parentheses.

Table II. Experimental Liquid Heat Capacities, C_p

	Temperature (K)								
	350	360	370	380	390	400	410	420	430
Methyl p-aminobenzoate						74.6[a]	76.1	77.9	78.6
						(2.0)[b]	(1.2)	(2.5)	(0.6)
Ethyl p-aminobenzoate			79.8	81.0	81.4	82.9			
			(1.4)	(1.4)	(1.9)	(2.1)			
n-Propyl p-aminobenzoate		87.5	88.3	89.4	90.0	90.6			
		(0.8)	(0.9)	(0.4)	(1.7)	(2.1)			
n-Butyl p-aminobenzoate	93.5	94.8	95.7	97.5					
	(0.3)	(0.6)	(0.6)	(1.5)					
n-Nonyl p-aminobenzoate		138	140	143	146				
		(5)	(3)	(4)	(3)				

	355	365	375	385	395
n-Pentyl p-aminobenzoate	101	102	104	105	106
	(3)	(3)	(2)	(3)	(3)
n-Hexyl p-aminobenzoate		115	117	118	120
		(2)	(2)	(2)	(1)

[a] Mean heat capacity in cal/(mol*deg).

[b] Standard deviation in parentheses.

RESULTS

The heat capacity of the solid form of a compound, in general, increases with respect to temperature at a rate equal to or greater than the liquid form heat capacity, as can be seen in Tables I and II. Little is known of the heat capacities of the supercooled liquid form of organic compounds, that is, the liquid form of the compound at temperatures below its normal melting point. There are two logical assumptions that can be considered. The first is that, in a plot of heat capacity as a function of temperature as seen in Fig. 3, the supercooled liquid heat capacities will be collinear with the heat capacities of the liquid form of the compound. This assumption would result in a ΔC_P which increases as the temperature of comparison is removed further from the melting point. The alternate assumption is that the supercooled liquid form would consistently have a heat capacity higher than the solid form heat capacity by the difference between the solid and the liquid heat capacities at the melting point, as shown in Fig. 3. The latter assumption gives a constant ΔC_P and is assumed here. The value of ΔC_P at the melting point, which is reported in Table III, was determined by generating a straight-line relation for the solid phase heat capacities as a function of temperature, and a second straight line for the liquid phase heat capacities, and extrapolating each line to the melting point. The difference in heat capacity at the melting point between these extrapolated lines was determined and assigned to ΔC_P. The results from these experiments on the *n*-alkyl para-aminobenzoates are given in Table III. Other pertinent data from the literature are given in Table IV.

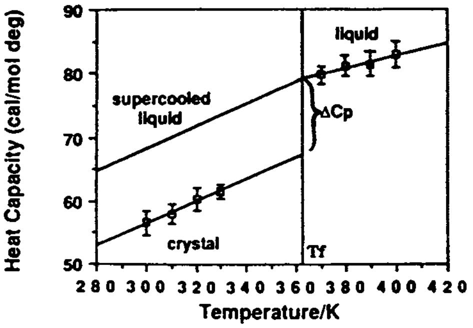

Fig. 3. Plot of the heat capacities of solid and liquid ethyl para-aminobenzoate showing the assumed heat capacities of the supercooled liquid.

DISCUSSION

The alternative, simplifying assumptions involving ΔC_P in ideal solubility estimations are extreme approximations, and actual ΔC_P values lie between them, as seen from the

Table III. A Comparison of the Change in Heat Capacity with the Entropy of Fusion for *n*-Alkyl Para-aminobenzoates

		(cal/mol deg)			
Ester	T_f/K	$C_{p,s}$	$C_{p,l}$	ΔC_p	ΔS_f
Methyl	385.2	61.0 (±0.7)[a]	72.7 (±0.7)	11.6 (±1.4)	14.0
Ethyl	362.9	67.3 (±0.6)	79.1 (±0.6)	11.8 (±1.2)	14.7
n-Propyl	346.6	79.5 (±0.1)	86.5 (±0.3)	7.1 (±0.4)	14.2
n-Butyl	331.1	82.2 (±0.6)	91.0 (±0.5)	8.83 (±1.2)	14.8
n-Pentyl	325.5	83.4 (±0.2)	97.2 (±0.6)	13.8 (±0.8)	17.6
n-Hexyl	334.2	95.3 (±0.6)	110.2 (±0.6)	14.9 (±1.2)	23.7
n-Nonyl	343.4	120.7 (±0.8)	133.2 (±0.8)	12.5 (±1.6)	30.8

[a] 95% confidence interval, equal to 1.96 times the standard error of the estimate for the regression line from mean heat capacities; 95% confidence interval for ΔC_p is the sum of the solid and liquid intervals.

Table IV. A Comparison of the Change in Heat Capacity with the Entropy of Fusion from Literature Data

			(cal/mol deg)			
Compound	Ref.	T_f/K	$C_{p,s}$	$C_{p,l}$	ΔC_p	ΔS_f
Aromatic hydrocarbons						
Benzene	17	278.7	30.25	31.45	1.20	8.46
Naphthalene	18	353.4	49.74	52.05	2.31	12.83
Anthracene	19	488.9	85.14	86.62	1.48	14.35
Acenaphthene	20	366.6	61.78	62.83	1.05	13.99
Fluorene	20	387.9	70.33	70.37	0.04	12.06
Phenanthrene	20	372.4	67.82	71.60	3.78	10.57
Toluene	17	178.2	21.45	32.15	10.70	8.90
Ethylbenzene	17	178.2	25.48	37.28	11.80	12.32
n-Propylbenzene	17	173.6	28.87	43.03	14.16	12.76
o-Xylene	17	247.8	34.58	41.33	6.75	13.11
m-Xylene	17	225.3	29.77	38.60	8.83	12.27
p-Xylene	17	286.4	37.63	42.40	4.77	14.28
1,2,3-Trimethyl Bz[a]	17	247.8	43.32	47.65	4.33	7.89
1,2,4-Trimethyl Bz	17	229.3	36.45	46.07	9.62	12.01
1,3,5-Trimethyl Bz	17	228.4	35.20	44.02	8.82	9.94
1-Methylnaphthalene	18	242.7	37.07	48.35	11.28	6.84
2-Methylnaphthalene	18	307.7	49.03	54.37	5.34	9.42
Biphenyl	13	342.2	54.74	64.17	9.43	12.99
Diphenyl ether	21	300.0	52.00	64.10	12.10	13.72
Cyclohexylbenzene	13	280.5	52.01	60.29	8.28	13.03
Benzyl alcohol	23	257.9	33.82	44.71	10.89	8.31
Triphenylmethane	22	365.3	93.87	106.5	12.62	14.36
Dibenzothiophene	13	371.0	58.17	66.93	8.76	13.91
Alkanes						
n-Hexane	17	177.9	29.39	40.40	11.01	17.58
n-Heptane	17	182.6	34.40	47.43	13.03	18.39
n-Octane	17	216.4	41.58	54.96	13.38	22.91
2-Methylhexane	17	154.9	31.89	42.60	10.71	14.17
2-Ethylpentane	17	154.6	30.36	41.04	10.68	14.77
2,2-Dimethylpentane	17	149.3	32.16	38.98	6.82	9.32
Miscellaneous						
Methylamine	23	179.8	14.30	23.48	9.18	8.14
Dimethylamine	23	181.0	18.60	28.92	10.32	7.84
Trimethylamine	23	156.1	22.59	27.38	4.79	10.03
Dimethylhydrazine	22	216.0	22.33	36.36	14.03	11.15
Isopropylmercaptan	22	142.6	25.07	31.33	6.26	9.61
t-Butylmercaptan	22	274.3	36.37	40.66	4.29	2.16
Amylmercaptan	22	197.5	33.23	44.52	11.29	21.22
Methylnitrate	22	190.2	23.40	31.43	8.03	10.36
Ethyl Acetate	23	189.6	27.57	37.44	9.87	13.20
1-Bromo-octane	22	218.2	44.22	62.34	18.12	27.04
Chlorotrifluoroethene	22	115.0	17.48	26.64	9.16	11.54
Furan	22	187.5	19.65	23.77	4.12	4.85

[a] Bz, benzene.

data in both Table III and Table IV. These tables list the heat capacity of each solid form at the melting point, $\Delta C_{P,s}$, the heat capacity of each liquid form at the melting point, $\Delta C_{P,l}$, and the corresponding ΔC_P values. The respective entropies of fusion for these compounds are included in Tables III and IV for comparison purposes.

As seen in Table III, ΔC_P is relatively close to ΔS_f for methyl and for ethyl para-aminobenzoate. While the ΔS_f values for the *n*-propyl and *n*-butyl esters are of the same magnitude as the shorter alkyl esters, the corresponding experimental ΔC_P is considerably smaller. There is no ready answer for the disparity between ΔC_P and ΔS_f for these two esters. The entropy of fusion remains higher than the experimental ΔC_P for the higher esters, *n*-pentyl through *n*-nonyl, but here we begin to see the definite pattern of an increase in ΔS_f due to the flexibility afforded the alkyl chain by melting.

It can be seen in Table IV that, for compounds that are rigid, such as benzene and the polycyclic aromatic hydrocarbons, ΔC_P is indeed closer to zero than to the entropy of fusion. This statement supports the interpretation by Yalkowsky (6) of the results of McLaughlin and Zainal (14) on the temperature dependence of the solubility of polycyclic aromatic hydrocarbons in benzene. The solutes included naphthalene, phenanthrene, fluorene, and anthracene, all of which are relatively rigid molecules. These solutes were assumed by Yalkowsky to form ideal solutions in benzene. After comparing the statistical correlation of the data with each equation, Eq. (2) and Eq. (3), Yalkowsky concluded that Eq. (2) provided a closer fit to the data, and therefore the assumption that ΔC_P equals zero is the better choice. But the flexibility made available for such compounds through melting is limited and ΔC_P, therefore, is expected to be small. Rotation of the whole molecule, however, may become available through melting. Andrews and Ubbelohde (15) have computed the volume requirement for rotation of the whole molecule about its principal axes. Their conclusion is that most of these rigid aromatics do not have sufficient room to rotate freely in the liquid state. Frank (16) noted that if the volume per molecule in the liquid state does not allow individual molecules to rotate freely, though, it may still be possible for two molecules to rotate together as a unit. This bimolecular rotation in the liquid state would preserve somewhat more than half of the rotational entropy difference available due to melting because the moment of inertia has doubled.

As can be seen from Tables III and IV, for compounds that are not rigid, the value of ΔC_P is better approximated by the entropy of fusion. The attachment of a flexible methyl group to the rigid molecule of benzene gives toluene where ΔC_P takes a value close to the entropy of fusion. Indeed, replacement of a benzene hydrogen with almost any functional group results in a compound where ΔC_P is better approximated by the entropy of fusion than by zero. Steric hindrance to intramolecular flexibility from the placement of functional groups results in a lessened heat capacity difference, as in the case of 1,2,3-trimethylbenzene, as opposed to 1,2,4- or 1,3,5-trimethylbenzene.

It should be kept in mind that the increase in heat capacity of the liquid form over the crystal form is possible through increases in freedom such as rotation of the entire molecule, vibrations, rotations about bonds, or wagging or flexing of bonds in the liquid form that were not possible in the crystal structure. If a simplifying assumption must be made for the differential heat capacity of organic molecules, enough data are provided in Tables III and IV to illustrate that, except for flat, rigid molecules, ΔC_P is better approximated by the entropy of fusion than by a value of zero.

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