Thermochimica Acta, 154 (1989) 27–47
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SOLUBILITIES AND SOLUTION THERMODYNAMICS OF SEVERAL SUBSTITUTED MELAMINES *

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(Received 12 December 1988)

ABSTRACT

A model for predicting solubility is proposed that involves summing two equilibrium processes which represent each step in the solution mechanism of a solid. In this model, hydrocarbon solubility is utilized as the measure of the crystalline energies.

Fourteen of the sixteen substituted melamine analogs used in this study were synthesized and their solubilities were determined as a function of temperature. Partition coefficients were measured between isooctane and water and differential scanning calorimetry experiments were performed. The thermodynamic quantities associated with the dissolution process were determined. This information was used to compare the proposed model with a model that uses the melting point as a measure of the energetics in the crystalline state.

The results suggest that the melting point may not always reflect appropriately the crystalline energies due to the possibility of hydrogen bonding or other specific interactions in the melt. The melting point has also been shown to be less sensitive than hydrocarbon solubility to changes in molecular structure, suggesting that the melting point is more difficult to interpret qualitatively. Hydrocarbon solubility appears to be a reliable alternative to the melting point for measuring the crystalline energies.

INTRODUCTION

The solubility of a medicinal agent is an important physical property. In many instances, solubility may be the controlling factor in the choice of a suitable dosage form or delivery system for a drug. Solubility may also dictate the performance of the drug in a particular dosage form as well as influence its biological activity. For these reasons, the ability to estimate the solubility of a drug in various solvents from changes in its molecular

* Dedicated to Professor James J. Christensen in memory of his contribution to innovation in calorimetry.

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0040-6031/89/$03.50

structure would enable the pharmaceutical chemist to incorporate desirable formulation, biopharmaceutical and distributive properties into a drug [1,2].

The ability to predict the solubility of a drug in a solvent is dependent on the ability to quantitate the various solute–solute, solvent–solvent and solvent–solute interactions involved in the solution process. For organic solids, it is necessary to have a knowledge of the energy required to remove a molecule from the crystal lattice and a knowledge of the energy required to solvate the molecule once removed. Since there are already a number of methods [3,4] available for estimating the energy necessary to solvate a molecule once removed from the crystal lattice, it seemed reasonable to investigate more extensivly methods for estimating the energetics in the solid state.

The principle objective of this research involves the development of a method for estimating solubilities of organic solids, including the quantitation of the solute–solute interactions in the solid state. There are at least two popular methods available for use in predicting the solubility of organic solids in various solvents. The older method was developed by Hildebrand et al. [5] and is based on the concept of internal pressure differences between the solvent and solute. Another method of predicting the solubility of solids was developed by Yalkowsky and Valvani [6]. This method uses the supercooled liquid melt as the reference state for the activity of the solute and the melting point as the measure of the crystal lattice energies; it is described by eqn. (1)

$$-\ln X = \Delta S_f (T_{mp} - T)/R + \ln PC_X \quad (1)$$

where ΔS_f (e.u.) is the entropy of fusion, X is the mole fraction solubility, T_{mp} (K) is the temperature at the melting point, T (K) is the temperature of the system and PC_X is the octanol–water mole fraction partition coefficient.

In this study, a method of predicting solubility is proposed in Fig. 1 that involves summing two equilibrium processes which represent each step in the solution mechanism of a solid [7,8]. This method uses hydrocarbon solubility as the measure of the crystalline energies and an infinitely dilute solution in a hydrocarbon solvent (e.g. isooctane) as the reference state for the activity of the solute.

Hydrocarbon solvents interact with the solute primarily through dispersion and inductive forces. These non-specific solute–solvent interactions are often considered to be relatively insensitive to subtle changes in the structural features of the solute and, for this reason, most differences observed in the hydrocarbon solubility for a series of structurally related compounds (e.g. analogs and prodrugs) can be attributed primarily to specific and non-specific interactions in the solid state [9,10].

Term A in Fig. 1 is defined as the thermodynamic activity of the drug in the solid state and represents the removal of the molecule from the crystal lattice. Values for this term can be obtained from the mole fraction solubil-

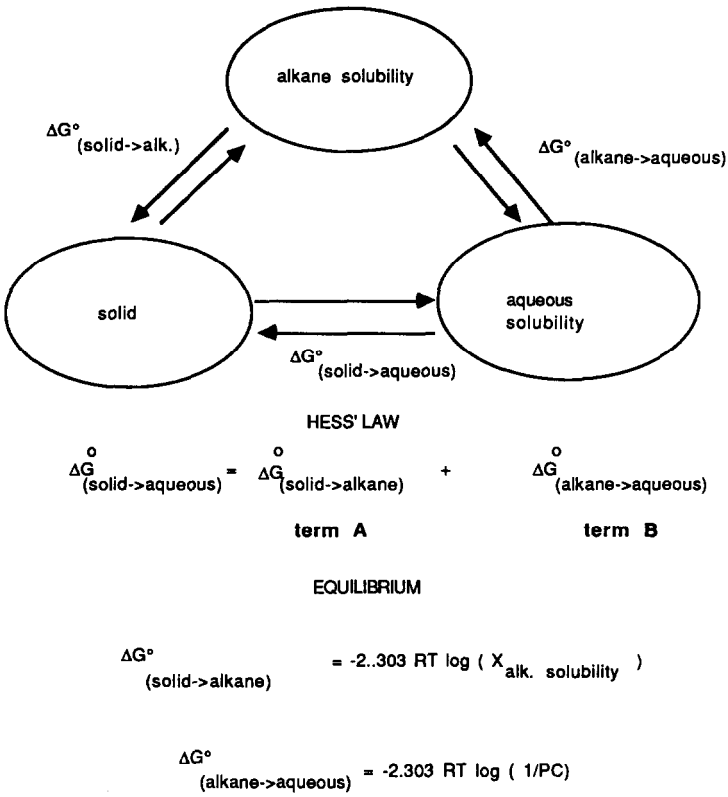


Fig. 1. Schematic illustration of the method described by eqn. (2) to predict the solubility of a solid in an aqueous solvent.

ity in a hydrocarbon solvent. Term B in Fig. 1 is defined as the free energy of transfer and represents the hydration of the molecule once removed from the crystal lattice [11]. Values for this term can be obtained from the inverse partition coefficient in a hydrocarbon–water system. Summing terms A and B (Fig. 1) results in eqn. (2)

$$-\log X_{aq} = -\log PC_X + \log X_{alk} \quad (2)$$

where X_{aq} is the mole fraction solubility in an aqueous solvent, PC_X is the alkane–water mole fraction partition coefficient and X_{alk} is the mole fraction solubility in an alkane solvent.

The study reported here is designed to compare the activity derived from the supercooled liquid melt reference state and the activity obtained using the reference state based on an infinitely dilute solution in isooctane. The two reference states are further evaluated by comparing the two methods of predicting solubility utilizing activities for the solid derived from either isooctane solubility (eqn. (2)) or the melting point (eqn. (1)). Both methods are correct from a thermodynamic standpoint but differ in the reference

state used for the activity of the drug in the crystalline phase. In addition, thermodynamic data derived from solubility vs. temperature experiments are used to evaluate the mechanism of solution of the 16 substituted melamine analogs studied. These solubilities are determined in 1-octanol, isooctane and an aqueous solvent.

MATERIALS AND METHODS

Materials and equipment

All chemicals were of analytical or reagent grade and were used without further purification. The water used in the synthetic procedures and the solubility and partition coefficient studies was deionized and charcoal filtered.

Separation of the product mixtures obtained from synthetic reactions was carried out on a Harrison Research model 7924T chromatotron using 60 F-254 silica adsorbent. Thin layer chromatography was performed on Kodak precoated silica sheets with a fluorescent indicator. ^{1}H-NMR spectra were run on a Varian T-60 instrument. The solvent for NMR analysis was deuterated chloroform (Aldrich, Milwaukee, WI) and tetramethylsilane was used as an internal standard. Melting points were taken in capillary tubes and were not corrected.

A Corning 150 pH meter was used for pH measurements. UV absorbance measurements were made with a Perkin–Elmer 555 spectrophotometer using Fisher quartz cuvettes. Thermal analysis was carried out on a Perkin–Elmer model DSC-4 differential scanning calorimeter. Samples for thermal analysis were weighed on a Cahn 21 microbalance.

Description of synthetic procedures

Fourteen of the sixteen substituted melamine analogs (listed in Table 1) used in this study required syntheses. The syntheses were carried out by reacting a nucleophilic amine in a basic aqueous medium with 2-chloro-4,6-bis-(dimethylamino)-2-triazine (SM) to form the product of interest. The starting material (SM) was synthesized according to the procedure described by Banks and Pearlman [12]. Compounds **3**, **5**, **6**, **7** and **16** were synthesized according to the procedures described by Borkovec and De Milo [13]. Compounds **4**, **8** and **9** were prepared according to the procedures described by Cumber and Ross [14]. Compounds **10**, **11**, **12**, **13**, **14** and **15** were synthesized according to procedures A–F respectively. The synthetic procedures A–F were developed in our laboratories.

The 16 substituted melamine analogs were purified by recrystallization from a suitable solvent and/or by column (flash chromatography, 60 mesh

silica) or centrifugal chromatography. The purity was established by DSC analysis and thin layer chromatography using 3 : 1 cyclohexane : ethyl acetate as the mobile phase. The molecular structures were determined by ^{1}H-NMR and mass spectrometry (Chemistry Department, University of Kansas). Elemental analysis (Midwest Microlabs, Indianapolis, IN) was performed for synthesized compounds not found in the literature. All of the qualitative data generated on the compounds used in the study were in agreement with the molecular structure.

*Procedure A (compound **10**)*

Piperazine (0.85 g, 0.01 mol) and SM (1 g, 0.005 mol) were added to 25 ml of distilled water. After stirring at room temperature overnight the mixture was filtered and the solid recrystallized from 1 N aqueous NaOH. Melting point 106–109 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.9–3.6 (m, 4), 3.1 (s, 12), 3.0–2.7 (m, 4), 2.1 (s, 1). Mass spectrometry, M^+ 251. Analysis: calculated for $C_{11}N_7H_{21}$: C, 53.59%; N, 39.04%; H, 8.36%; found: C, 53.42%; N, 38.69%; H, 8.34%.

*Procedure B (compound **11**)*

1-Methyl piperazine (1 g, 0.01 mol) and SM (1 g, 0.005 mol) were added to 25 ml of 1 N aqueous NaOH. The reaction mixture was refluxed for 1 h, after which it was allowed to cool to room temperature. The product mixture was extracted with chloroform and the organic phase was evaporated to dryness with nitrogen. The solid residue was recrystallized from 1 N aqueous NaOH. Melting point 80–81 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.0–3.6 (t, 4), 3.1 (s, 12), 2.5–2.3 (t, 4), 2.3 (s, 3). Mass spectrometry M^+ 265. Analysis: calculated for $C_{12}N_7H_{23}$: C, 49.07%; N, 31.34%; H, 7.46%; found C, 49.07%; N, 31.12%; H, 7.41%.

*Procedure C (compound **12**)*

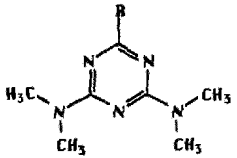
N-Methylphenethylamine (1.4 g, 0.01 mol) and SM (1 g, 0.005 mol) were added to 25 ml of 1 N aqueous NaOH. The mixture was refluxed for 1 h, after which it was allowed to cool to room temperature. The product mixture was extracted with chloroform and the collected organic phase was evaporated to dryness under nitrogen. The solid residue was recrystallized from ethanol–water. Melting point 59–62 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.4–7.0 (m, 5), 4.0–3.6 (m, 2), 3.1 (s, 12), 3.0 (s, 3), 3.0–2.8 (m, 2). Mass spectrometry M^+ 300. Analysis: calculated for $C_{16}N_6H_{24}$: C, 63.97%; N, 27.98%; H, 8.05%; found: C, 63.88%; N, 27.60%; H, 8.41%.

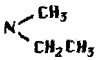
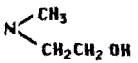
*Procedure D (compound **13**)*

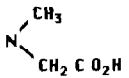
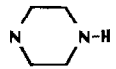
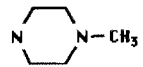
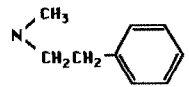
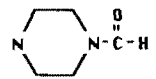
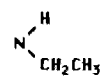
Thiomorpholine (1 g, 0.01 mol) and SM (1 g, 0.005 mol) were added to 25 ml of 1 N aqueous NaOH. The mixture was refluxed for 1 h, after which it was allowed to cool to room temperature. The product mixture was extracted

TABLE 1

The molecular structures and chemical names of the compounds used in the study (the numbers correspond to the compound number)



Compound	Chemical name	Fragment (R)
1	1,3,5-Tris(dimethylamino)-s-triazine	
2	1-(Methylamino)-3,5-bis(dimethylamino)-s-triazine	
3	1-(Methylamino)-3,5-bis(dimethylamino)-s-triazine	
4	1-(Ethanolamino)-3,5-bis(dimethylamino)-s-triazine	
5	1-(Pyrrolidinyl)-3,5-*bis*(dimethylamino)-s-triazine	
6	1-(Piperidinyl)-3,5-*bis*(dimethylamino)-s-triazine	
7	1-(Morpholinyl)-3,5-bis(dimethylamino)-s-triazine	

8	1-(Hydroxylamino)-3,5-bis(dimethylamino)-s-triazine	
9	1-(Sarcosino)-3,5-bis(dimethylamino)-s-triazine	
10	1-(1-Piperizinyl)-3,5-bis(dimethylamino)-s-triazine	
11	1-(4′-Formyl-1-piperizinyl)-3,5-bis(dimethylamino)-s-triazine	
12	1-(Methylphenethylamino)-3,5-bis(dimethylamino)-s-triazine	
13	1-(Thiomorpholinyl)-3,5-bis(dinmethylamino)-s-triazine	
14	1-(4′-Formyl-1-piperizinyl)-3,5-bis(dimethylamino)-s-triazine	
15	1-(Hexamethyleneimine)-3,5-bis(dimethylamino)-s-triazine	
16	1-(Ethylamino)-3,5-bis(dimethylamino)-s-triazine	

with chloroform. The collected chloroform was evaporated to dryness with nitrogen. The solid was recrystallized from ethanol–water. Melting point, 116–119°C. ^{1}H-NMR ($CDCl_3$) δ: 4.3–4.0 (m, 4), 3.1 (s, 12), 2.8–2.4 (m, 4). Mass spectrometry, M^+ 268. Analysis: calculated for $C_{11}N_6H_{20}S$: C, 49.25%; N, 31.34%; H, 7.46%; found: C, 49.07%; N, 31.12%; H, 7.41%.

*Procedure E (compound **14**)*

1-Piperazine-carboxaldehyde (1.1 g, 0.01 mol) and SM (1 g, 0.005 mol) were added to 25 ml of 1 N aqueous NaOH. This mixture was refluxed for 1 h, after which it was allowed to cool to room temperature. The product mixture was extracted with chloroform. The volume of the collected chloroform was reduced by evaporation under nitrogen. This solution was introduced onto the chromatotron where separation took place using 3:1 cyclohexane:ethylacetate as the mobile phase. The separated product was further purified by recrystallization from cyclohexane. Melting point, 185–188°C, ^{1}H-NMR ($CDCl_3$) δ: 8.1 (s, 1), 3.9–3.2 (m, 8), 3.1 (s, 12). Mass spectrometry, M^+ 279. Analysis: calculated for $C_{12}N_7H_{21}$: C, 51.60%; N, 35.13%; H, 8.24%; found: C, 51.56%; N, 34.99%; H, 8.04%.

*Procedure F (compound **15**)*

Hexamethyleneimine (1 g, 0.01 mol) and SM (1 g, 0.005 mol) were added to 25 ml of 1 N aqueous NaOH. The mixture was refluxed for 1 h, after which it was allowed to cool to room temperature. The product mixture was extracted with chloroform. The collected organic phase was evaporated to dryness with nitrogen. The solid was recrystallized from ethanol–water. Melting point 61–63°C. ^{1}H-NMR ($CDCl_3$) δ: 3.8–3.6 (m, 4), 3.1 (s, 12), 1.9–1.3 (br, 8). Mass spectrometry, M^+ 264. Analysis: calculated for $C_{13}N_6H_{24}$: C, 59.06%; N, 31.78%; H, 9.15%; found: C, 58.76%; N, 31.52%; H, 9.39%.

Solubility experiments

The mole fraction solubilities of the 16 substituted melamine analogs were determined in aqueous and hydrocarbon solvent systems at several temperatures. The temperature baths were controlled to ± 0.1°C. The aqueous solvent system consisted of a 0.05 M sodium borate buffer at pH 8.0 for compounds **1–9** and **12–16** and 0.1 N NaOH for compounds **10** and **11**. At pH 8.0, all the substituted melamine analogs (except **9**) were unionized as estimated from their pK_a values of approximately 5.0 [15]. The hydrocarbon solvent system for all compounds consisted of 1-octanol (Aldrich, Milwaukee, WI) or HPLC grade isooctane (Aldrich).

Excess amounts of the solid material were equilibrated in 1–2 ml of solvent in 2 ml Teflon-lined screw-capped vials. Once equilibrium was established the suspensions were passed through 0.22 μm disposable filters

(Centaur Sciences) and appropriately diluted (after weighing) for UV absorbance measurements on a spectrophotometer. The filtrate was deposited into a test-tube resting in a water bath at the temperature of the sample suspension. This was done in an effort to avoid precipitation prior to dilution. The aqueous solubilities of **12** and **15** were determined using the facilitated dissolution method described by Higuchi et al. [7].

A small amount of the solid in equilibrium with the solution was removed for DSC analysis to check for any changes in the crystal morphology over the temperature range used in obtaining the van't Hoff plots. It was determined that there was no significant adsorption of the compounds onto the filters and that only one stable crystal form existed for a particular compound over the temperature range and solvents studied.

Partition coefficient experiments

Partition coefficients PC_X were determined for each compound at 25 °C. The aqueous solvents for the partitioning systems were the same as used in the solubility studies. Partitioning systems were first thoroughly mixed using an apparatus designed for liquid–liquid extractions and for preparing emulsions. After mixing, the two immiscible solvents were allowed to separate in a temperature-controlled (± 0.1 °C) water bath overnight. No centrifugation of the separated solvents was considered necessary prior to analysis due to the low solubility of isooctane in water. The isooctane and aqueous phases were assayed separately after an appropriate dilution. The method of analysis was UV absorbance.

A back extraction involving the aqueous phase was employed for compounds **12** and **15** because of their low activities in water relative to isooctane. Compound **9** required concentration of the isooctane layer prior to the spectrophotometric assay because of its low activity in isooctane relative to water.

Differential scanning calorimetry (DSC) experiments

Samples (3–6 mg) for DSC analysis were weighed on an electronic microbalance (Cahn 21) in an aluminum pan which was crimp sealed with a lid. Compound **1** was sealed in a special pan for volatile liquids. Each compound was studied at scan rates of 5, 10 and 20 °C min^{-1}. These scans were started at least 30 °C below the melting temperature of the pure solid. Nitrogen was purged through the system at a flow rate of 20 lbf in^{-2} min^{-1}. An empty pan with a lid was used as the control for all DSC runs.

The reported ΔH_f values were obtained by extrapolation to zero heating rate and to the corresponding melting point T_m obtained by equating it to the endotherm's temperature onset value T_o. The reference compound for the enthalpy calculations was indium ($T_m = 156.6$, $\Delta H_f = 7.0$ cal g^{-1}).

RESULTS AND DISCUSSION

The difference in the sign of ΔS_{soln} (Tables 2 and 3) in water and isooctane suggests that the compounds dissolve via different mechanisms in the two solvents. The values for ΔS_{soln} are positive for all compounds in isooctane and reflect minimal solvent–solute interactions in the hydrocarbon system. However, the ΔS_{soln} values in the aqueous systems are

TABLE 2

Solution thermodynamic values in a borate buffer or 0.1 N aqueous NaOH (compounds **10** and **11**)

Compound	ΔH_{soln} (cal mol^{-1})	ΔS_{soln} (cal mol^{-1} K^{-1})	ΔG_{soln} (cal mol^{-1})
1	−1800	−29.7	7040
	(200)	(0.7)	(8)
2	−1400	−21.8	5100
	(250)	(0.9)	(20)
3	−2380	−33.3	7530
	(230)	(0.8)	(30)
4	1200	−12.9	5030
	(65)	(0.1)	(50)
5	−1910	−31.7	7540
	(360)	(1.2)	(20)
6	−3620	−37.3	7500
	(360)	(1.2)	(8)
7	1140	−17.4	6320
	(90)	(0.3)	(35)
8	2880	−9.1	5590
	(120)	(0.4)	(9)
9			3920
			(20)
10	1160	−13.1	5060
	(120)	(0.4)	(20)
11	2370	−10.8	5590
	(110)	(0.3)	(60)
12	1030	−32.6	8680
	(510)	(1.7)	(80)
13	−470	−25.9	8180
	(870)	(2.9)	(40)
14	460	−17.6	5710
	(380)	(1.3)	(20)
15	980	−26.0	8720
	(700)	(2.1)	(60)
16	640	−15.6	5300
	(450)	(1.5)	(14)

Values in parentheses are the standard deviations.

TABLE 3

Solution thermodynamic values in isooctane

Compound	ΔH_{soln} (cal mol^{-1})	ΔS_{soln} (cal mol^{-1} K^{-1})	ΔG_{soln} (cal mol^{-1})
1	5660	11.0	2380
	(440)	(1.5)	(8)
2	6800	14.6	2440
	(500)	(1.7)	(12)
3	4810	11.1	1510
	(500)	(1.7)	(30)
4	5510	9.2	2770
	(490)	(1.6)	(4)
5	5190	9.7	2300
	(280)	(0.9)	(4)
6	7610	20.5	1500
	(130)	(0.5)	(17)
7	5870	11.2	2510
	(310)	(1.2)	(190)
8	10500	24.5	3150
	(540)	(1.8)	(40)
9	7620	7.4	5410
	(420)	(1.4)	(2)
10	10810	24.9	3370
	(850)	(2.9)	(16)
11	6300	14.3	2040
	(750)	(2.6)	(30)
12	10660	32.3	1040
	(830)	(2.8)	(30)
13	5140	8.6	2570
	(50)	(0.2)	(20)
14	5820	3.6	4760
	(400)	(1.4)	(60)
15	4980	13.4	990
	(420)	(1.4)	(30)
16	8780	24.9	1370
	(490)	(1.6)	(70)

Values in parentheses are the standard deviations.

negative for all compounds, indicating extensive structuring of water around the dissolved solute [16] or extensive solute–solvent interactions.

The data in Fig. 2 suggest that the solution process in isooctane is enthalpy dominated and that the dissolution of the solids in water is entropy controlled, except for compound **8**. Compounds **9** and **14** have a significantly larger enthalpy contribution to hydrocarbon solubility. For these compounds, the process of forming a solution in an inert hydrocarbon solvent such as isooctane should result in significant hydrogen-bond breaking in the system as reflected in the increase in the total enthalpy change ΔH.

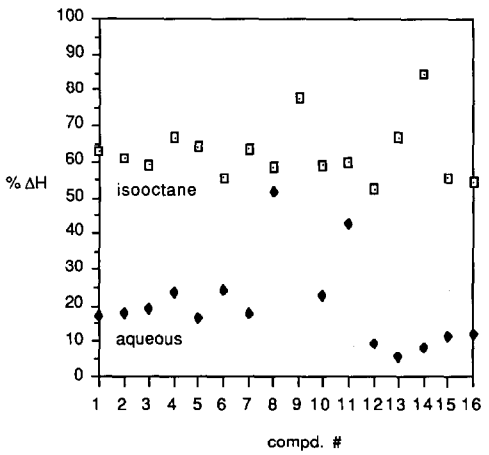


Fig. 2. Schematic illustration of the percentage enthalpy contribution ($\%\Delta H$) to the total free energy of solution for each compound studied in isooctane and in 0.1 M borate buffer (pH 8.0). Compounds **10** and **11** were studied in 0.1 N aqueous NaOH.

Thermodynamic values were also obtained in 1-octanol for a few selected compounds and are listed in Table 4. As expected, compounds not capable of hydrogen bonding in the solid phase or in solution have similar solubilities in 1-octanol and isooctane. However, compounds **8**, **9**, **10** and **14** have solubilities in 1-octanol which are significantly greater than in isooctane. This is possibly due to the presence of the solvent's hydroxyl group. Evidence of this nature suggests that solubility in 1-octanol not only reflects interactions in the solid, but specific interactions with the solvent molecules.

TABLE 4

Solution thermodynamic values in 1-octanol

Compound	ΔH_{soln} (cal mol^{-1})	ΔS_{soln} (cal mol^{-1} K^{-1})	ΔG_{soln} (cal mol^{-1})
1	6830	15.4	2240
	(330)	(1.1)	(25)
3	7040	17.8	1720
	(440)	(1.5)	(20)
8	8140	19.3	2390
	(440)	(1.5)	(50)
9	6360	13.7	2270
	(600)	(2.0)	(15)
10	4100	7.1	1960
	(280)	(0.9)	(50)
14	7040	14.0	2870
	(950)	(3.4)	(50)

Values in parentheses are the standard deviations.

Therefore, the difference in the solubilities of the compounds in 1-octanol is much less than that observed in isooctane. These results illustrate the inability of 1-octanol solubility to reflect solid state energies adequately relative to isooctane solubility.

If the supercooled liquid melt is used as the reference state for the activity of the solute, it is possible to calculate certain thermodynamic values using eqns. (3)–(7) [17]

$$G^{\text{soln}} - G^{\text{ideal}} = -592 \ln X_{\text{iso}}^{25\,^\circ\text{C}} + \Delta S_{\text{f}}/1364(T_{\text{m}} - 25) \tag{3}$$

$$H^{\text{soln}} - H^{\ominus} = RT \ln(a/X) \tag{4}$$

$$(S^{\text{soln}} - S^{\ominus})^{\text{r}} = \Delta S_{\text{soln}} - \Delta S_{\text{f}} + R \ln a \tag{5}$$

$$(S^{\text{soln}} - S^{\ominus})^{\text{i}} = -R \ln X_{\text{iso}}^{25\,^\circ\text{C}} \tag{6}$$

$$R \ln a = \Delta S_{\text{f}} \ln(T/T_{\text{m}}) \tag{7}$$

$G^{\text{soln}} - G^{\text{ideal}}$ is the excess free energy of solution, $S^{\text{soln}} - S^{\text{ideal}}$ is the excess entropy of solution, $H^{\text{soln}} - H^{\ominus}$ is the enthalpy of mixing, $(S^{\text{soln}} - S^{\ominus})^{\text{r}}$ is the entropy associated with the transfer from the melt phase to solution, $(S^{\text{soln}} - S^{\ominus})^{\text{i}}$ is the entropy associated with the transfer from the melt phase to an ideal solution, ΔS_{f} is the entropy of fusion (Table 5), ΔS_{soln} is the entropy of solution, $X_{\text{iso}}^{25\,^\circ\text{C}}$ is the mole fraction solubility in isooctane at 25 °C, a is the activity of the solute, X is the mole fraction solubility of the solute and T_{m} is the melting temperature (Table 5). The thermodynamic values obtained using the above equations (except eqn. (7)) are listed in Tables 6 and 7.

The differences between solute–solvent, solvent–solvent and solute–solute intermolecular forces in a regular solution are sufficiently small for thermal motion to keep molecules randomly dispersed in the system. For this reason, a convenient way to assess whether a solution is regular or not is to observe whether the entropy determined experimentally is equivalent to the entropy calculated for an ideal solution. If we choose the supercooled melt as the reference state for the activity of the solute, the non-zero values observed for the excess entropy of solution ($S^{\text{soln}} - S^{\text{ideal}}$) indicate that the solutions of the substituted melamine analogs in isooctane and 1-octanol are not regular. Therefore, it appears that specific interactions when present are more important than the bulk properties of the pure solid and solvent in determining the solubility of a drug in an organic solvent [18]. Furthermore, the observed positive non-zero values for the enthalpy of mixing ($H^{\text{soln}} - H^{\ominus}$) in Table 6 and 7 indicate that solutions in isooctane and 1-octanol are also non-ideal [5].

Since isooctane is considered to be an inert solvent that interacts non-specifically with the solute, the negative $S^{\text{soln}} - S^{\text{ideal}}$ values observed for the majority of compounds studied must reflect the specific and non-specific

TABLE 5

Thermodynamic values from differential scanning calorimetry

Compound	ΔH_f (cal mol^{-1})	ΔS_f (cal mol^{-1} K^{-1})	T_{mp} (°C)
1	5500	12.3	171.2
	(180)		(0.9)
2	5340	14.1	105.6
	(100)		(0.3)
3	5090	13.3	110.8
	(20)		(0.3)
4	4140	11.1	100.1
	(100)		(0.3)
5	6120	15.2	129.9
	(70)		(1.0)
6	5550	15.4	88.3
	(240)		(0.7)
7	5900	14.8	124.2
	(240)		(0.5)
8	7330[a,b]	19.2	108.3
9	7130[a,b]	16.6	157.8
10	5500	14.4	108.8
	(320)		(0.9)
11	4880	13.8	81.0
	(180)		(0.2)
12	4790	14.3	61.0
	(70)		(0.6)
13	6950	17.8	118.0
	(530)		(0.6)
14	7400[a]	16.1	186.7
	(50)		(0.6)
15	3900	11.6	62.6
	(25)		(0.5)
16	4000	12.0	59.8
	(55)		(0.7)

Values in parentheses are the standard deviations.

[a] Compounds thought to exist as polymorphs.

[b] Value obtained from one determination.

TABLE 6

Calculated thermodynamic values in 1-octanol

Compound	$(S^{soln} - S^{\ominus})^r$	$S^{soln} - S^{ideal}$	$H^{soln} - H^{\ominus}$
1	−1.8	−9.3	780
3	1.1	−4.6	720
8	−4.6	−12.6	1010
9	−9.0	−16.6	450
10	−10.9	−18.1	1100
14	−9.1	−18.7	790

TABLE 7

Calculated thermodynamic values in isooctane

Compound	$(S^{soln} - S^{\ominus})^r$	$S^{soln} - S^{ideal}$	$H^{soln} - H^{\ominus}$	$G^{soln} - G^{ideal}$
1	−6.2	−14.2	910	580
2	−2.4	−10.6	1570	1100
3	−5.6	−10.6	510	370
4	−4.4	−13.7	2030	1930
5	−10.1	−17.8	940	700
6	2.1	−2.9	620	530
7	−7.9	−16.3	1240	1040
8	0.6	−10.0	1740	1550
9	−15.3	−33.5	3590	3210
10	6.9	−4.4	2300	2160
11	−1.9	−8.7	1340	1270
12	16.4	12.9	560	530
13	−14.0	−22.6	1120	910
14	−19.5	−35.4	2650	2160
15	0.4	−2.9	580	550
16	11.6	6.9	980	950

interactions present in the melt. Other indicators of interactions in the melt are the large positive values of $H^{soln} - H^{\ominus}$ observed for compounds **9**, **10** and **14** in isooctane which may be interpreted as reflecting the breaking of hydrogen bonds on transfer from the melt phase to solution in an inert solvent [10].

The negative $S^{soln} - S^{ideal}$ values for the six compounds studies in 1-octanol increase relative to their values in isooctane (except **8**), while the large positive $H^{soln} - H^{\ominus}$ values observed in isooctane for the hydrogen-bonding compounds are significantly smaller in 1-octanol. This observation suggests that 1-octanol more closely resembles the melt phase of these solids than does isooctane and, for this reason, octanol is a better solvent than isooctane for use in the method described by eqn. (1).

The melting point is often considered to be a measure of the crystal lattice energies, but in Fig. 3 there appears to be only a weak free energy relationship between it and isooctane solubility. The poor correlation is particularly evident for compounds that are capable of hydrogen bonding in the solid state. In other words, the specific interactions present exert an effect in both the melt and the solid phase, making any melting point differences difficult to interpret qualitatively [19]. For instance, the hydrocarbon solubility of compound **8** is lower than the hydrocarbon solubility of compound **1** but the melting point of **1** is 63°C higher than the melting point observed for **8**. Apparently, specific interactions in the melt phase of compound **8** offset the higher melting temperature of solid **1**.

If hydrocarbon solubility only reflects interactions in the solid phase, then interactions in the melt may be responsible for the observation in Fig. 3 that

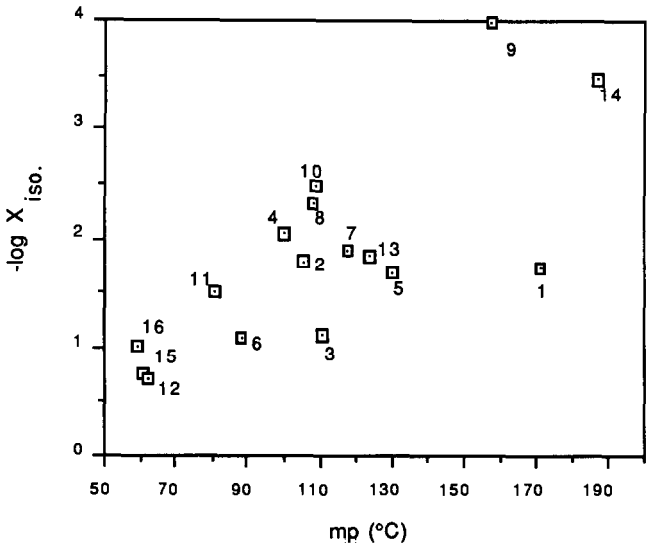


Fig. 3. Plot of the logarithm of solubility in isooctane at 25 °C vs. the melting point (m.p.). The numbers correspond to the compound number.

compounds melting in the narrow range of 100–110 °C exhibit a greater than 20-fold difference in their isooctane solubilities. This also suggests that isooctane solubility is more sensitive to structural changes than the melting point.

Figure 4 shows a plot of the solute activity derived using the hypothetical supercooled liquid melt as the standard state vs. the activity obtained from solubility measurements in isooctane using a 1 M solution in isooctane as the standard state. It is apparent from the slope that the activity obtained using the supercooled liquid melt as the standard state is significantly less sensitive to structural changes than the activity derived from solubility measurements in isooctane. This is based on the observation that when isooctane solubility changes by three orders of magnitude, the activity using the supercooled liquid melt standard state changes by only one order of magnitude.

Figure 5 shows the solubilities predicted using the model defined by eqn. (1) and Fig. 6 shows the solubilities predicted using the model defined by eqn. (2). The linear regression correlation coefficients support the usefulness of both equations in estimating aqueous solubilities. It is interesting, however, that a statistically significant intercept and a slope of larger than unity are observed when using eqn. (1). This may indicate a phenomenon unaccounted for in eqn. (1) or it may be due to the fact that eqn. (1) was originally developed for use with octanol–water partition coefficients and not isooctane–water systems.

Multiple linear regression was performed on the equilibrium data in Tables 5 and 8 to statistically compare hydrocarbon solubility and the

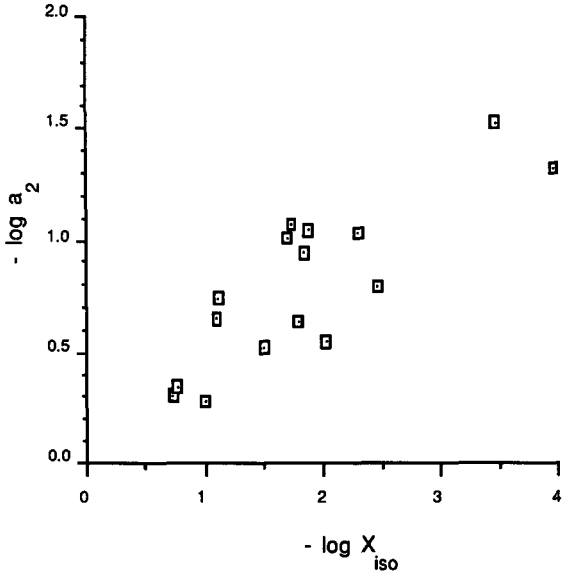


Fig. 4. Log–log plot of the activity calculated using the supercooled liquid melt as the reference state (eqn. (7)), i.e. log a_2, vs. the activity determined using an infinitely dilute solution in isooctane as the reference state (log X_{iso}).

melting point as measures of crystalline energies. The results in Tables 9 and 10 show that the coefficient for the melting point is approximately two orders of magnitude smaller and statistically less significant than the coeffi-

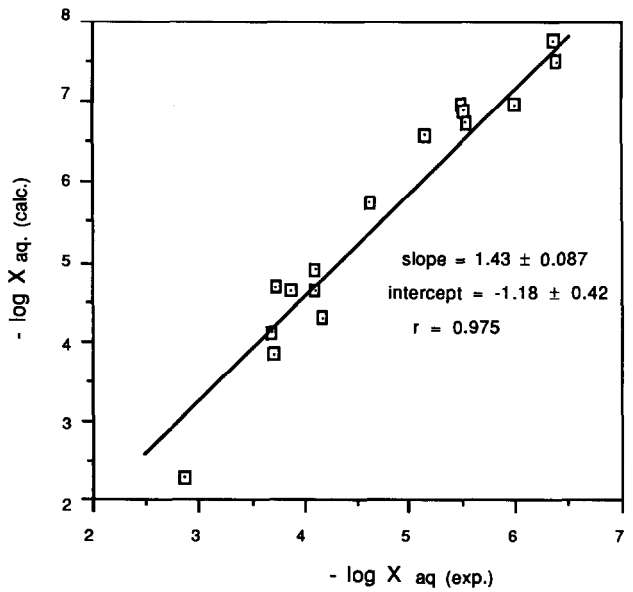


Fig. 5. Log–log plot of the aqueous solubilities calculated using eqn. (1) vs. the experimentally determined aqueous solubilities at 25 °C.

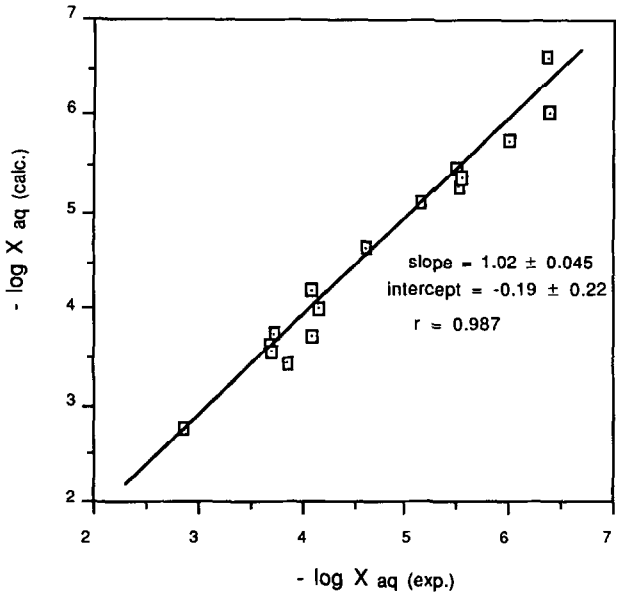


Fig. 6. Log–log plot of the aqueous solubilities calculated using eqn. (2) vs. the experimentally determined aqueous solubilities at 25 °C.

TABLE 8

Mole fraction solubilities (−log) in water and isooctane and water–isooctane partition coefficients PC at 25 °C

Compound	$-\log X_{aq}$ [a]	$-\log X_{iso}$ [a]	$\log PC_X$ [a]
1	5.16	1.74	3.39
2	3.74	1.79	1.95
3	5.52	1.11	4.17
4	3.69	2.03	1.61
5	5.53	1.69	3.68
6	5.50	1.10	4.38
7	4.63	1.84	2.80
8	4.10	2.31	1.88
9	2.87	3.97	−1.22
10	3.71	2.47	1.08
11	4.09	1.50	2.21
12	6.36	0.765	5.51 [b]
13	5.99	1.88	3.88
14	4.18	3.47	0.54
15	6.39	0.726	5.32 [b]
16	3.88	1.01	2.43

[a] Reproducible within 5%.
[b] Reproducible within 20%.

TABLE 9

Multiple linear regression analysis of the results using the melting point model (eqn. (1))

Variable	Coefficient	Std. dev.	t	Prob. $> t$ (10^5)
Constant	2.028	3.773	5.373	22.5
Melting point	0.00812	0.00248	3.279	557.0
log PC_X	0.653	0.0519	12.57	0.171

TABLE 10

Multiple linear regression analysis of the results using the proposed model in Fig. 1 (eqn. (2))

Variable	Coefficient	Std. dev.	t	Prob. $> t$ (10^5)
Constant	0.514	0.296	1.738	10100
$-\log X_{iso}$	0.869	0.0939	0.9256	0.783
log PC_X	0.953	0.0473	20.13	0.0294

cient determined for $-\log X_{iso}$. For this reason, it may be appropriate to conclude from the regression analysis that the hydrocarbon solubilities reflect the crystal lattice energies more appropriately than do the melting temperatures of the solids evaluated in this study.

CONCLUSIONS

The equilibrium solubility studies and the derived thermodynamic information in the hydrocarbon solvent isooctane indicate that the mechanism of solution in isooctane for the substituted melamine analogs studied does not involve significant intermolecular interactions between the solute and solvent. This is based on the observation that the solution entropy change is positive for all compounds evaluated in isooctane.

The equilibrium solubility studies and the derived thermodynamic information in the aqueous solvents indicate that the solution of the substituted melamine analogs in water is entropy dominated, i.e. the major contributor to the free energy of solution is the entropy term ($T\Delta S$) and not the enthalpy. In addition, the structuring of water molecules around the dissolved solute is considered to be responsible for the large negative solution entropy change observed in the aqueous solvents.

The study by Martodihardjo [20] suggests that the melting point is an appropriate measure of crystal lattice interactions for a homologous series of non-polar compounds. However, for compounds that hydrogen bond in the solid state, the melting point may not reflect appropriately the crystalline energies due to the possibility of hydrogen bonding in the melt phase. The thermodynamic data obtained using the supercooled liquid melt as the

reference state for the activity of the solid supports this conclusion if the negative excess entropy of solution ($\Delta S_{excess} < 0$) calculated for the solutions in isooctane is a reflection of specific interactions (i.e. hydrogen bonding) in the melt phase. The melting point of a solid has also been shown to be less sensitive than hydrocarbon solubility to changes in the molecular structure, suggesting that the melting point is more difficult to interpret qualitatively and therefore not as well suited to a group contribution approach.

The melting point, by definition, is the temperature at which the escaping tendency (m) in the solid equals the escaping tendency in the melt, and so at best the melting point only measures the crystalline energies at the melting temperature. In fact, the free energy of fusion ΔG_f at the melting temperature ($\Delta G_f = 0$ at melting temperature) does not always equal the ΔG_f value at the temperature of the solubility measurement [21]. Hydrocarbon solubility, on the other hand, appears to be a reliable alternative to the melting point, supporting the usefulness of the model in Fig. 1 for predicting the solubility of organic solids in water.

ACKNOWLEDGEMENTS

Partial support was provided by Ortho Pharmaceutical Corporation and NIH Grant GM33387. We also acknowledge helpful suggestions from Dr. Val Stella of the University of Kansas.

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