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Accounting for the Effects of Moderately Increased Pressure on the Energetics of Melting and Solubility in Metered Dose Inhalers

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The purpose of this study is to account for thermodynamic variations due to changes in the physical environment of propellant-based systems, particularly metered dose inhalers (MDIs). Twenty organic compounds were measured via differential scanning calorimetry under ambient pressure, 60 psi, and 90 psi. The increase in pressure did not affect the melting point of any of the compounds. A modest increase (~8%) in enthalpy of fusion was noted. This correlates to a modest increase in entropy of fusion, and thus ideal crystalline solubility, though the magnitude of this change depends primarily on the melting point of the given compound. Because the relationship between melting point and solubility is logarithmic, compounds with higher melting points are affected more by this increased energy of melting. Based on the findings, modest changes can be made to predictive models to estimate solubility in propellant systems to account for changes in the physical environment of MDIs.

Keywords metered dose inhaler; propellant; solubility; pressure; hydrofluoroalkane; 134a; 227

INTRODUCTION

Inhalation drug therapy is a mainstay in today's medical society. Pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD) are primarily treated using aerosols delivered from nebulizers, dry powder inhalers, and even more commonly, metered dose inhalers (MDIs). MDIs have been used since the late 1950s when epinephrine MDIs became available. At that time, chlorofluorocarbons (CFCs) were the propellants of choice; however, later research discovered the deleterious effects that CFCs posed to the environment (Molina & Rowland, 1974). As such, suitable replacement propellants were needed as the Montreal Protocol called for a widespread discontinuation of CFC use.

Two potential replacements were identified in hydrofluoroalkane (HFA) 227 (1,1,1,2,3,3,3-heptafluoropropane) and 134a (1,1,1,2-tetrafluoroethane). These HFA propellants proved to display suitable characteristics with regard to toxicity and in general, environmental factors; however, they display quite different chemical characteristics as compared with their CFC predecessors (McDonald & Martin, 2000). The vapor pressure exerted is similar to that of CFC 12 (dichlorodifluoromethane), but is much higher than both CFC 11 (trichlorofluoromethane) and 114 (dichlorotetrafluoroethane), both of which were used primarily as cosolvents in propellant mixes with CFC 12, which provided the driving force for aerosolization.

Despite HFA propellants becoming widely accepted substitutes for CFCs, chemical compatibility has proven significantly different. Several researchers report that many previously used excipients and solutes behave very differently (McDonald & Martin, 2000; Ridder, Davies-Cutting, & Kellaway, 2005; Smith, 1995; Smyth, 2003; Stein & Stefely, 2003; Vervaet & Byron, 1999). Other studies are underway attempting to understand and describe these differences (Hoye, Gupta, & Myrdal, 2007). Hoye et al. investigate the structure–property relationship between HFA 134a and a series of organic compounds. Additionally, excipients have been investigated and designed specifically for their use in HFA systems (Stefely, 2002). Despite the increase in scientific understanding of these systems, progress has been slow due to the relative difficulty of analyzing MDIs. Recently however, analytical methodologies have been offered that may facilitate conduction of these studies. (Gupta & Myrdal, 2004a, 2004b, 2005; Mogalian, Kuehl, & Myrdal, 2007; Traini, Young, Price, & Rogueda, 2006).

As an initial step in understanding miscibility in HFAs, accounting for changes in the physical environment relative to ambient conditions needs to be addressed. As such, the purpose of this study is to examine the effects of moderately

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TABLE 1
Compound List with Corresponding (Onset) Melting Temperature in Ambient Conditions, Transition Temperature (Denoted by ‘tr’), and Molecular Weight

Compound	T_m (K)	MW (g/mol)
1,2-Benzanthracene	434.25	228.29
Benzo[*a*]pyrene	447.55	252.31
(tr)	376.99	
Chrysene	539.50	228.29
Fluorene	387.65	166.22
Hexamethylbenzene	438.65	162.27
(tr)	384.23	
Pentachlorophenol	462.55	266.34
(tr)	350.20	
Phenanthrene	371.25	178.23
Salicylic acid	432.35	138.12
4-Nitrochlorobenzene	356.15	157.56
1,2,4,5-Tetrachlorobenzene	413.25	215.89
1,2,3-Trichlorobenzene	325.61	181.45
1,3,5-Trichlorobenzene	335.82	181.45
Caffeine	509.59	194.19
(tr)	414.85	
Naphthalene	353.65	128.18
2-Naphthol	393.87	144.17
1-Naphthoic acid	434.79	172.18
1-Naphthylacetic acid	401.22	186.21
(tr)	368.86	
2-Naphthyl acetate	341.97	186.21
1-Nitronaphthalene	329.45	173.17
1-Naphthalene methanol	332.96	158.2

increased pressure, similar to that seen in MDIs, on the energetics of melting and thus ideal crystalline solubility (X_u^{ideal}) of organic solids. This evaluation is paramount for developing predictive models for solid solute solubilities in HFA propellants. In this investigation, 20 organic compounds of varying structural properties were analyzed using differential scanning calorimetry (DSC) for measurement of melting point and enthalpy of fusion (ΔH_m), which enabled calculation of entropy of fusion (ΔS_m) under ambient conditions, then under moderately increased pressure comparable to those exerted by HFA 227 and 134a (60 and 90 psi, respectively) (Table 1).

BACKGROUND

Ideal crystalline solubility prediction, and corresponding thermodynamic descriptions have been well documented (Yalkowsky, 1999). Utilizing the Clausius–Clapeyron equation, applying Kirchoff’s law stating that the energy of an irreversible process is equal to the energy of three reversible processes between the same end points, and noting that total Gibbs free energy equals 0 at the melting or transition temperature, yields Equation 1,

$$\log X_u^{\text{ideal}} = \frac{-\Delta S_{\text{tr}}(T_{\text{tr}}-T)}{2.303RT} + \frac{\Delta C_p^{\text{ss}}}{2.303R}\left(\frac{T_{\text{tr}}-T}{T} - \ln\frac{T_{\text{tr}}}{T}\right) - \frac{\Delta S_m(T_m-T)}{2.303RT} + \frac{\Delta C_p^{\text{ls}}}{2.303R}\left(\frac{T_m-T}{T} - \ln\frac{T_m}{T}\right), \tag{1}$$

where T_{tr} or T_m refer to the solid–solid phase transition or melting, respectively, ΔC_p^{ss} or ΔC_p^{ls} refers to the change in heat capacity between two solid (transition) phases or the liquid and solid phases, respectively, at an experimental temperature, T. Indeed, the ideal solubility from Equation 1 offers the complete thermodynamic cycle, however, because there are no reliable methods for calculating or simply estimating $\Delta C_p^{\text{ls/ss}}$, they will be assumed ≈0. By assuming $\Delta C_p \approx 0$, theoretically ideal crystalline solubility could be slightly underestimated for higher melting compounds; however, several studies support its utility in comparison to experimental data (Yalkowsky & Valvani, 1980). Further debate (assuming that $\Delta C_p \approx \Delta S_m$) may be warranted, but is of limited additional utility when the compounds of interest melt at relatively lower temperatures, as is the case in this study. Using the former assumption, Equation 1 simplifies to Equation 2.

$$\log X_u^{\text{ideal}} = \frac{-\Delta S_m(T_m-T)}{2.303RT} - \frac{\Delta S_{\text{tr}}(T_{\text{tr}}-T)}{2.303RT} \tag{2}$$

This form can be further simplified by applying Walden’s rule stating that the entropy of melting (ΔS_m) for organic compounds can be approximated at 6.79R (~56 J/K/mol). Also, it could be assumed that $\Delta S_{\text{tr}} \approx 0$ because either a solid–solid transition does not exist, as is the case for the majority organic compounds (and is shown again later in this manuscript), or the entropic change is small compared with that of ΔS_m, and can be considered negligible. Utilizing these assumptions and reducing mathematically (also assuming ambient temperature is 25°C) yields Equation 3, which only requires the melting point (in °C) to approximate a compounds ideal crystalline solubility.

$$\log X_u^{\text{ideal}} = -0.01(\text{MP} - 25) \tag{3}$$

Again, the primary concern of this study is to determine what effect moderately increased pressure has on a given crystal structure and its propensity to melt, which in turn effects solubility. Upon establishment of the enthalpic and entropic changes of compounds under pressure, further investigations can be initiated examining the structure–behavior relationship between organic compounds and HFA propellants to ultimately yield a predictive relationship describing the entire system, analogous to that has been completed for organic compounds in an aqueous system, as described by Equation 4, the general solubility equation (Yalkowsky, 1999).

$$\log S_{\mathrm{w}} = 0.5 - 0.01(\mathrm{MP} - 25) - \log K_{\mathrm{ow}} \quad (4)$$

METHODS

DSC (Model Q1000, TA Instruments, New Castle, DE, USA) was conducted using a pressure cell for determination of melting point (T_{m}), enthalpy of fusion (ΔH_{m}), and ultimately entropy of fusion (ΔS_{m}). The compounds were measured at 3 pressures of interest, ambient (~14.7 psi [1 atm]), 60 psi, and 90 psi. The later pressures were chosen to encompass the vapor pressures which would be typically found in hydrofluoroalkane formulations. HFA 227 has a vapor pressure of 56.6 psi at 25°C and 134a has a vapor pressure of 83 psi at 25°C (Solkane Product Information).

Prior to testing, the DSC pressure cell was calibrated at each pressure of interest for baseline and cell constant calibration. Twenty organic compounds were used with various chemical properties and melting points ranging from 325 to 540 K, as listed in Table 1. The compounds were lightly ground with a mortar and pestle, and then accurately weighed (1.5–5 mg). Other than grinding, all compounds were used as received. Aluminum hermatic pans were topped with a pinhole containing lid to allow for pressure to be applied via nitrogen gas. An identical empty pan and lid served as the reference for enthalpy of fusion and melting point determination. Heating rate was the same for all compounds at 5°C/min to approximately 30°C greater than previously reported melting points for the given compounds. All compounds were supplied by Aldrich Chemical Company (Milwaukee, WI, USA) and Sigma Chemical Company (St. Louis, MO, USA).

RESULTS AND DISCUSSION

Figure 1 displays the melting point of the compounds at ambient pressure compared with the increased pressures. No change in melting point was noted over the span of pressures examined (average RSD = 0.2%, compounds measured $n = 3$). Other authors have noted shifts in melting temperatures, or shifts in phase transitions allowing for better resolution of multiple polymorphic crystal forms; however, in the cases noted, experimental pressures were 100- to 1000-fold higher that the experimental pressures applied here (Arntz & Schneider, 1980; Ledru, Imrie, Hutchison, & Hohne, 2006; Ledru, Imrie, Pulham, Ceolin, & Hutchison, 2007). As such, it appears that for the pressures of interest applied here, no adjustments to the melting or transition temperatures are necessary.

The average ΔS_{m} for the compounds at ambient pressure was 57.5 ± 14.3 J/mol/K, close to the 56 J/mol/K mentioned in the assumptions above. For compounds examined at 60 psi, average ΔS_{m} was 61.6 ± 12.2 J/mol/K, and 62.2 ± 12.6 J/mol/K at 90 psi. The entropy of melting results for each compound is individually displayed in Table 2. As seen in Figure 2, ΔS_{m}

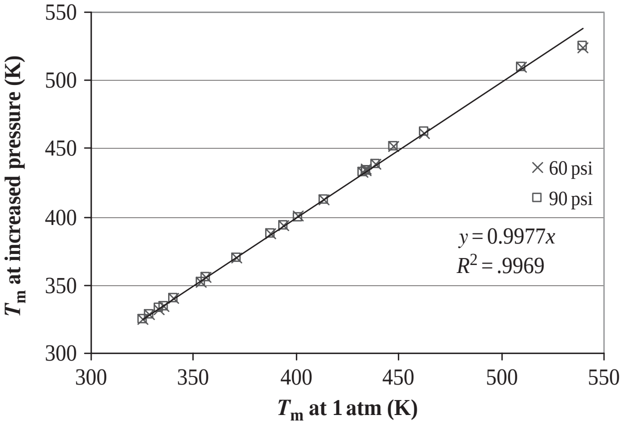

FIGURE 1. Melting temperature at increased pressures relative to ambient conditions.

TABLE 2
Average ΔS_{m} Measurements for Given Pressures of Interest

Compound	14.7 psi	60 psi	90 psi
1,2-Benzanthracene	54.10	57.54	67.07
Benzo[*a*]pyrene	29.77	41.21	43.61
(tr)	14.13	19.91	18.85
Chrysene	52.05	55.20	55.29
Fluorene	47.85	51.84	57.03
Hexamethylbenzene	53.05	73.51	59.50
(tr)	4.19	4.70	4.95
Naphthalene	53.28	60.49	62.24
Pentachlorophenol	33.80	39.69	37.11
(tr)	26.12	30.15	26.03
Phenanthrene	37.97	44.09	43.27
Salicylic acid	66.67	64.51	63.37
4-Nitrochlorobenzene	45.97	48.45	52.18
1,2,4,5-Tetrachlorobenzene	65.93	72.60	74.94
1,2,3-Trichlorobenzene	55.19	62.85	63.22
1,3,5-Trichlorobenzene	54.90	58.61	59.02
Caffeine	46.03	47.97	47.53
(tr)	7.23	7.87	8.18
2-Naphthol	61.19	61.30	59.61
1-Naphthoic acid	59.30	59.38	62.08
1-Naphthylacetic acid	104.00	94.77	101.00
(tr)	4.79	5.05	5.14
2-Naphthyl acetate	66.84	63.85	68.75
1-Nitronaphthalene	58.53	59.48	57.06
1-Naphthalene methanol	46.77	47.53	47.01

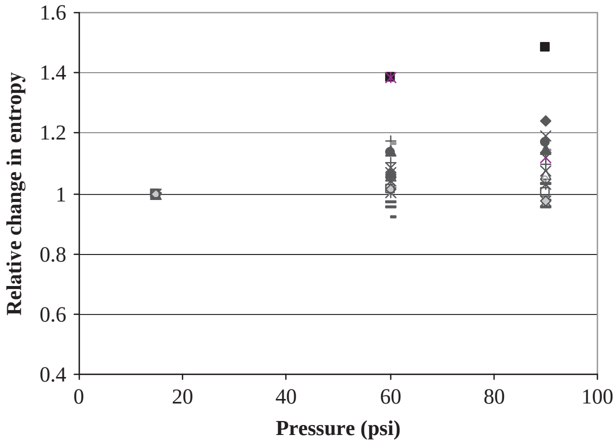

FIGURE 2. Relative change in ΔS_m compared with ambient conditions.

deviated positively for all compounds examined under increased pressure except a few compounds; salicylic acid, 1-naphthylacetic acid and 2-naphthol at 90 psi, which demonstrated a slight negative deviation in ΔS_m relative to those at ambient pressure.

For compounds examined at 60 psi, ΔS_m was on average approximately 7% greater than their respective compounds measured at ambient pressure. Likewise, for compounds examined at 90 psi, ΔS_m was on average approximately 8% greater than respective compounds measured at ambient pressure. Figures 3 and 4 demonstrate this entropic relationship, and a similar one can be seen when examining ΔH_m, because no change in melting point was noted.

Probing the effects this has on ideal crystalline solubility, theoretical calculations were conducted utilizing the experimentally determined ΔS_m compared with ambient conditions. These results can be seen in Figure 5. Using Equation 2 and the experimentally determined ΔS_m listed above, this theoretical extrapolation shows the impact of the increased ΔS_m on the ideal crystalline solubility (X_u^{ideal}).

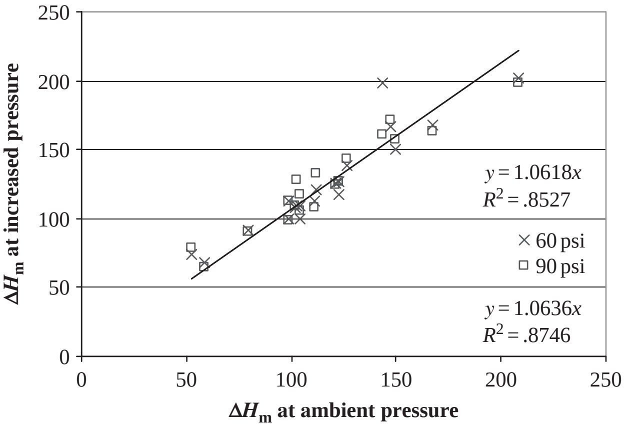

FIGURE 3. Change in ΔH_m at increased pressures relative to ambient conditions.

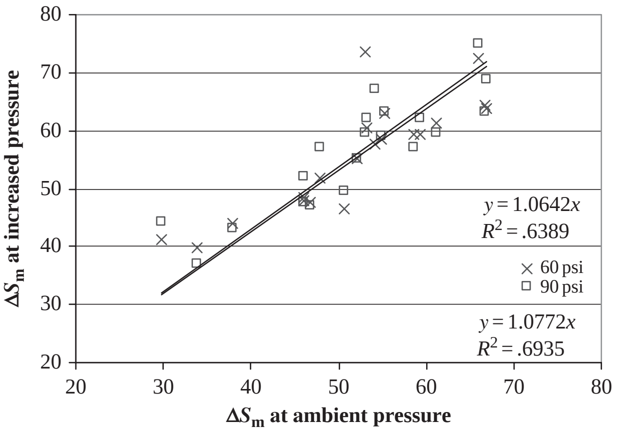

FIGURE 4. Change in ΔS_m at increased pressures relative to ambient conditions.

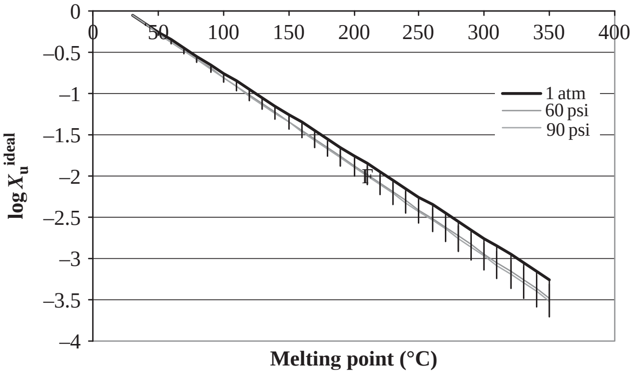

FIGURE 5. Theoretical extrapolation displaying ideal crystalline solubility decrease relative to melting point at ambient and increased pressure conditions. Standard deviations are of increased pressure conditions.

The calculations reveal a (theoretical) decline in ideal crystalline solubility (X_u^{ideal}) of approximately 30–35% at the mean and up to approximately 70–80% solubility decrease at +1*SD* (~0–10% at –1*SD*), compared with baseline pressure measurements for a compound with a melting point of 300°C. Yet due to the log-linear fashion of this relationship, compounds with lower melting points demonstrate a far smaller effect. For example, a compound that melts at 100°C would show a decrease in (X_u^{ideal}) of approximately 10–15% at the mean compared with baseline measurements.

Based on the above data, Equation 2 could be easily modified to include an adjustment based on this data by simply multiplying ΔS_m by 1.08, or for simplicity 1.1, which could approximate the examined range of pressures. Because Equation 1 includes a simplified version of Equation 2, the crystal term (–0.01(MP – 25)) could also be simply modified here to reflect the increased ΔS_m, as displayed in Equation 5, when attempting to estimate solubility in pressurized systems.

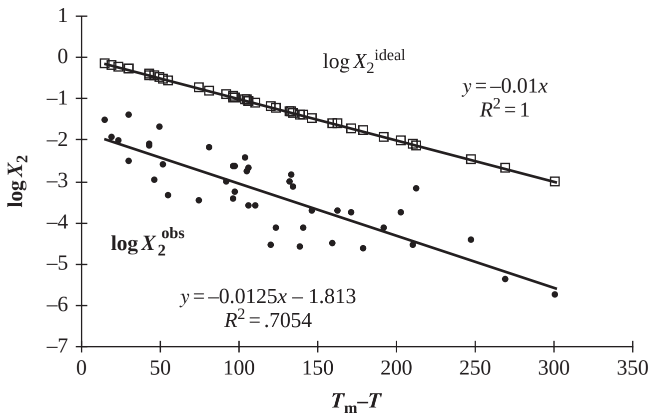

FIGURE 6. Ideal (log X^{ideal}) and experimental (log X^{obs}) solubility data extracted from Hoye et al., log X_2 expressed as mole fraction solubility, T_m and T are expressed in degrees Kelvin.

To use the entirety of Equation 4, however, the activity coefficient between the propellant and the solute would need to be investigated and an analogous equation used for estimation of solubility in a hydrofluoroalkane system, as described by Hoye et al. (2007).

$$\log X_u^{\text{ideal}} = -0.011(\text{MP} - 25) \tag{5}$$

Figure 6 displays data extracted from the literature with permission from Hoye et al. (2007), showing mole fraction solubility as a function of melting point. Of note is the fact that this solubility data includes many organic compounds, including some of the above compounds in HFA 134a (primarily naphthalene derivatives and chlorobenzenes). The study primarily examined the involvement of activity coefficient on solubility, addressing contributions from chemical interactions (partitioning, etc). The data displayed in Figure 6 supports the current study, showing ideal crystalline solubility as a function of melting point (note: activity coefficient is determined by the *y*-intercept, and the slope of the line indicates the contribution of ideal crystalline solubility). Despite these values being determined via solubility examination, the negative slope (–0.0125) is consistent with the data found here and suggest that the use of –0.011(MP – 25) is reasonable.

CONCLUSION

The intent of this study was to determine the effect that moderately increased pressure exerted by hydrofluoroalkane propellants 227 and 134a in a MDI system may have with respect to the energetics of melting and consequently ideal solubility. Twenty compounds underwent DSC at ambient pressure, as well as at 60 and 90 psi to simulate the vapor pressure exerted by the aforementioned HFAs. This resulted in an increased enthalpy and entropy of fusion of approximately 7–8%, with no change in melting point. This correlates to a theoretical solubility change dependent on the melting point of a compound due do the log-linear relationship, with higher melting compounds theoretically experiencing a more pronounced decrease in ideal crystalline solubility.

Thus, for compounds that have a low melting point, the change in ideal crystalline solubility should be negligible, and therefore no change needs to be made in theoretical calculations of the crystal term to account for pressure. However as the melting point increases for the compound of interest, the more significant this change in entropy becomes, and a correction should be utilized to more accurately estimate ideal crystalline solubility. The results were also supported by an independent study, and despite the independence of the testing methods and metrics, a remarkably similar relationship was noted. In summary, a simple modification can be made to account for the changes noted in the physical environment when attempting to estimate solubility of organic compounds in propellant systems.

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