

Predicting the Total Entropy of Melting: Application to Pharmaceuticals and Environmentally Relevant Compounds

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Abstract □ Experimental entropy of melting values for physical property estimation schemes, such as solubility and vapor pressure, are not readily available. In this study a semiempirical equation, which contains two molecular parameters, is used to estimate the total entropy of melting for a variety of pharmaceutically and environmentally relevant compounds. A database of experimental entropy values consisting of over 370 different compounds was compiled from literature. A molecular rotational symmetry number and a molecular flexibility number for each compound were defined. The simple equation does very well in predicting the total entropy of melting for the complex set of molecules with an average error of 21%.

Introduction

The physicochemical properties of compounds are important in many fields, including the pharmaceutical and environmental sciences. Property estimations can help to minimize time and cost in drug formulation development. They are also useful in assessing exposure limits for new chemical entities. Aqueous solubility and vapor pressure are among the most important of these properties. These properties can be estimated by the rearrangement of the Clausius–Clapeyron equation. For instance, the following equation can be used to predict the ideal mole fractional solubility:¹

$$\log X_i = [-\Delta H_m(T_m - T)/(2.3RT_m T)] - \Delta C_p/R[\Delta H_m(T_m - T)/(2.3T) + \log(T_m/T)] \quad (1)$$

where ΔH_m is the enthalpy of melting, ΔC_p is the heat capacity difference between the crystalline and the molten form, R is the gas constant, T and T_m are temperature and the melting point in Kelvin. This equation can be simplified to:

$$\log X_i = -\Delta S_m(T_m - T)/(2.3RT) \quad (2)$$

by replacing $\Delta H_m/T_m$ with ΔS_m , the entropy of melting, and assuming that ΔS_m is large compared to ΔC_p .

As can be seen from eqs 1 and 2, the melting point and either the enthalpy of melting or the entropy of melting are required. Unfortunately, the values of the two latter parameters are usually not readily available. The entropy of melting can either be assumed to be a constant (by Walden's rule or Richard's rule) or estimated from structure. Walden's rule is based on aromatic hydrocarbons

while Richard's rule is applicable to small, spherical molecules. There are two types of structure-based estimation schemes found in the literature: group contribution methods such as those of Chickos and co-workers^{2,3} and Domalski and Hearing,⁴ and the semiempirical equation of Yalkowsky and co-workers.^{5–8} The group contribution methods which employ tables of values for each group or fragment are cumbersome to use and some times have missing group fragments, whereas the semiempirical equation which uses two nonadditive molecular descriptors is easy to use and can be employed for all nonelectrolytes.

The following semiempirical equation was shown to work quite well in estimating the total entropy of melting for nonelectrolytes:^{5,8}

$$\Delta S_m^{\text{tot}} = 50 - R \ln \sigma + R \ln \phi \text{ J/deg}\cdot\text{mol} \quad (3)$$

where R is the gas constant in J/deg·mol, and σ and ϕ are the molecular symmetry and flexibility numbers which are defined below. The total entropy of melting includes entropies associated with solid–solid transitions, as well as the solid–liquid transition. In this paper the above equation is applied to a complex set of data for a wide range of pharmaceutical and environmental compounds.

Methods

Data—Experimental entropy of melting data, including the transitional entropies when reported, for pharmaceutically and environmentally relevant compounds are compiled from literature^{9–11} and entered into a database using dBASE IV. The database contains 413 entropy of melting values for 376 different compounds.

The database contains multiple entropy of melting values for some compounds. Since these values are reported by different authors they are treated as individual data points and are not averaged. Entropy of melting values that are less than 9 J/K·mol are considered to be unreasonably low and therefore omitted from the average calculations. Only five compounds consisting of six entropy of melting values have been omitted from the database based on this criteria.

The error associated with the prediction of the entropy melting in this paper is calculated by:

$$\text{error} = (\Delta S_m^{\text{obsd}} - \Delta S_m^{\text{pred}})/\Delta S_m^{\text{obsd}} \times 100 \quad (4)$$

where ΔS_m^{obsd} and ΔS_m^{pred} are the observed and predicted entropies of melting.

There is some overlap between the data set used in the earlier studies^{5,6} and the present data set. Only 48 of the 371 different compounds in the present data set were used in the previous studies. They are included here because of their biological relevance.

Molecular Flexibility Number—Increasing molecular flexibility increases the total entropy of melting. To account

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Table 1—Examples of Molecular Flexibility for Some Pharmaceutical and Environmental Compounds

| name | SP2 | SP3 | RING | ln ϕ |
|----------------------|-----|-----|------|-----------|
| cinnamic acid | 3 | 0 | 1 | 1.0 |
| butanoic acid | 1 | 2 | 0 | 1.6 |
| simazine | 0 | 4 | 1 | 3.7 |
| heptylcyclohexane | 0 | 6 | 1 | 5.8 |
| triacetin | 3 | 6 | 0 | 6.8 |
| decane | 0 | 8 | 0 | 7.3 |
| glycerol tristearate | 3 | 54 | 0 | 57.1 |

for the effects of flexibility on entropy of melting Dannenfelser and co-workers^{5,8} have defined a molecular flexibility number, ϕ , for flexible molecules. A flexible molecule contains at least one twist angle, which consists of a string of four non-hydrogen atoms that are not rotationally restricted. The number of twist angles can be calculated by subtracting 1 from the total number of chain atoms present in the molecule. Radially symmetrical end groups such as halogens and carbonyl oxygens are not counted as chain atoms because their rotation does not contribute to the molecule's flexibility. Methyl, primary amine, and hydroxy groups are assumed to be freely rotating and effectively radially symmetrical.

In calculating the molecular flexibility number, sp^2 and sp^3 chain atoms are assigned values of 0.5 and 1.0, respectively. Since the bonds between sp chain atoms do not contribute to flexibility, these atoms are assigned a value of zero. Ring systems, whether single or fused, are counted as a single group and assigned a value of 0.5 per system.

The molecular flexibility number for all molecules is given by:

$$\phi = 2.85^{[SP3 + 0.5SP2 + 0.5RING - 1]} \quad (5)$$

where SP3 is the number of sp^3 chain atoms, SP2 is the number of sp^2 chain atoms, and RING is the number of single or fused ring systems. It is important to note that the exponent is never less than zero. An exponent of zero indicates a rigid, nonflexible molecule so that ϕ equals unity and $\ln \phi$ equals zero, i.e.,

$$\ln 2.85^0 = 0 \quad (6)$$

Examples of some molecular flexibility numbers (shown as $\ln \phi$) for some pharmaceutical and environmental compounds are listed in Table 1 along with the values for the SP3, SP2, and RING designations.

Molecular Rotational Symmetry Number—Highly symmetrical molecules are known to have a lower entropy of melting than unsymmetrical molecules. Yalkowsky and co-workers^{6,7} have accounted for the effects of symmetry on entropy by defining a molecular symmetry number, σ . The following describes how these numbers are defined for individual molecules.

Since there are many ways in which a molecule can be oriented, one of these ways is arbitrarily chosen as the reference orientation. The number of orientations that are identical to the reference that are produced by rigid rotation, up to 360° about its center of mass, in both of the two spherical angles is defined as the molecular rotational symmetry number or σ . In assigning a value to σ , some groups, such as the halogens, carbonyl oxygen, and cyano, are assumed to be radially symmetrical. Again hydrogens are assumed to be freely rotating and not to contribute to molecular symmetry. Thus methyl, hydroxyl, mercapto, and primary amine groups are treated the same as halogens. Since every molecule has at least one identical

A: 1,4-dichlorobenzene B: 1-bromo-2-chlorobenzene

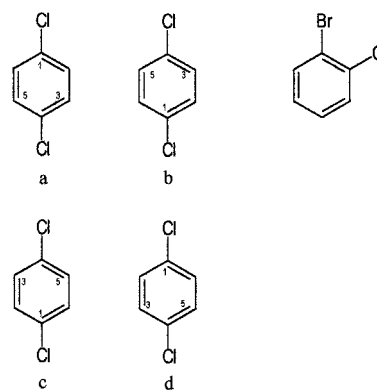


Figure 1—Examples of defining molecular symmetry numbers.

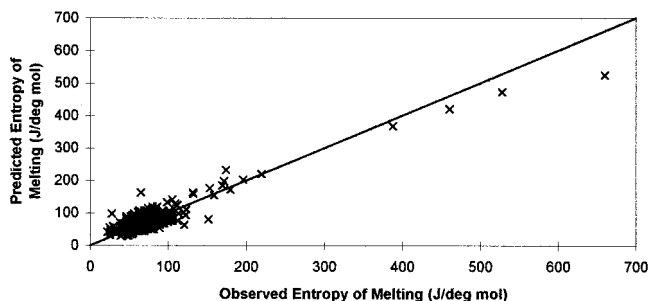


Figure 2—

orientation (produced by a 360° rotation about any axis), the molecular symmetry number is never less than unity (i.e., $\sigma \geq 1$). Thus flexible molecules are assigned a symmetry number of unity.

Molecules with one infinite rotational axis (i.e., cones and cylinders) and molecules with an infinite number of infinite rotational axes (i.e., spheres) have been empirically assigned effective symmetry numbers of 10 and 100, respectively.

Figure 1 shows how 1,4-dichlorobenzene and 1,2-bromo-chlorobenzene are assigned σ values. Assuming that "a" in Figure 1A is the reference orientation, three other orientations are identical to "a". These can be achieved by rotating "a" 180° about its horizontal axis to obtain "b" and by a 180° clockwise rotation of "a" and "b" to obtain orientations "c" and "d", respectively. Thus 1,4-dichlorobenzene has a molecular symmetry number of four ($\sigma = 4$). As shown in Figure 1B, 1-bromo-2-chlorobenzene, an unsymmetrical molecule, has a molecular symmetry number of unity ($\sigma = 1$) since only a 360° rotation about any axis results in an identical image.

Results and Discussion

The current model to predict the entropy of melting is limited to nonelectrolytes and assumes that the molecules do not self-associate to form dimers or other small aggregates. Only molecular symmetry and flexibility are accounted for in this model. Other factors can effect the entropy of melting, such as eccentricity.

Equation 3 with the molecular parameters, σ and ϕ , was used to predict the total entropy of melting for each compound. No additional parameters or coefficients are used. Figure 2 shows the observed versus predicted entropies of melting. Perfect fit is represented as the solid line with a slope of unity in the graph. As can be seen from the graph, eq 3 does well in predicting the total entropy of

Table 2—Total Entropy of Melting for Highly Flexible Compounds: Walden's Rule versus Eq 3

| name | $\Delta S_m^{\text{obsd}}/\Delta S_m^{\text{calcd}}$ (Walden) | $\Delta S_m^{\text{obsd}}/\Delta S_m^{\text{calcd}}$ (eq 3) |
|-----------------------------------|--|--|
| tridecanoic acid | 1.87 | 0.75 |
| myristyl alcohol | 2.82 | 1.03 |
| pentadecanoic acid | 2.34 | 0.83 |
| hexadecane (cetane) | 2.34 | 0.81 |
| hexadecanol (cetyl alcohol) | 3.19 | 1.05 |
| margaric acid | 2.71 | 0.87 |
| stearic acid | 3.00 | 0.92 |
| fenbutatin oxide | 3.04 | 0.87 |
| ethyl stearate | 3.47 | 0.97 |
| ethyl arachidate | 3.89 | 1.00 |
| chloramphenicol palmitate | 3.08 | 0.75 |
| glyceryl trilaurate | 6.87 | 1.06 |
| glyceryl trimyristate | 8.15 | 1.10 |
| glyceryl tripalmitate | 9.35 | 1.12 |
| tristearin (glyceryl tristearate) | 11.68 | 126 |
| average ratio | 4.52 | 0.96 |

melting for the complex set of compounds. The average error in predicting the entropy of melting is 21%. This is well within experimental error seen in the reported entropy of melting data. Experimental errors associated with measuring entropy of melting are reflected in the error of the calculated entropy of melting which are based on the measured values. Whenever possible, experimental values are preferred to calculated values.

A constant to estimate the total entropy of melting cannot be utilized well for those compounds that lie at extremes, i.e., molecules that are small and spherical and those that are highly flexible. Richard's rule was based on small, spherical molecules with an average entropy of melting of 10.5 J/deg mol. While Walden's rule, 56.5 J/deg mol, is an average of 17 entropies of melting for petroleum byproducts or aromatic hydrocarbons. All compounds of interest would have the same estimated entropy of melting when one of the constants are used. Since most pharmaceutical and environmental compounds are not small and spherical, Walden's rule would be chosen to predict the entropy of melting. To see the effect of using eq 3 versus a constant, the ratio of the observed over the predicted entropy of melting values are given in Table 2. A ratio of 1 indicates that the prediction is the same or very close to the observed value. Since the average ratio for eq 3 is close to 1, it predicts the total entropy of melting better than using Walden's rule, which has an average ratio of 4.5. The

difference between eq 3 and Walden's rule is more dramatic for molecules with a high degree of flexibility.

Conclusion

Equation 3 which uses only two molecular parameters, σ and ϕ , does very well in predicting the total entropy of melting for more than 370 complex pharmaceutical and environmental compounds. This equation results in an average error of 21% for 407 data points.

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