

# Two New Parameters for Predicting the Entropy of Melting: Eccentricity ( $\epsilon$ ) and Spirality ( $\mu$ )

Jennifer L. H. Johnson<sup>\*,†</sup> and Samuel H. Yalkowsky

Department of Pharmaceutical Sciences, The University of Arizona College of Pharmacy, 1703 E. Mabel Street, Tucson, Arizona 85721

The prediction of the entropy of fusion of organic compounds is studied. Rotational symmetry ( $\sigma$ ) and flexibility ( $\phi$ ) have already been shown to contribute to the orientational and conformational entropy of fusion, respectively. Eccentricity ( $\epsilon$ ) and spirality ( $\mu$ ) are two new parameters that influence translational and configurational entropy.  $\epsilon$  is defined as the ratio of the volume of a box around a rigid molecule to the cubed radius of a sphere containing the same molecular van der Waals volume.  $\mu$  is defined as the number of benzo[c]phenanthrene regions present in the molecule. This moiety results in repulsion and out of plane twisting to maximize the distance between hydrogens. Enthalpy of melting, melting point, and geometrical data for 117 compounds were gathered from the literature. The database consists of alkanes, polycyclic aromatic hydrocarbons, alkyl benzenes, and other alkyl aromatics. The addition of  $\epsilon$  and  $\mu$  to  $\sigma$  and  $\phi$  as predictors for the entropy of melting revealed a best fit melting point prediction line with a slope close to unity and a coefficient of determination ( $R^2$ ) of 0.90. In addition, the average absolute error of melting point estimation was improved from 90 K to 43 K. Hence, the newly defined  $\epsilon$  and  $\mu$  parameters offer significant improvement when combined with  $\sigma$  and  $\phi$  in the prediction of the entropies of melting and, consequently, melting points of organic molecules.

## Introduction

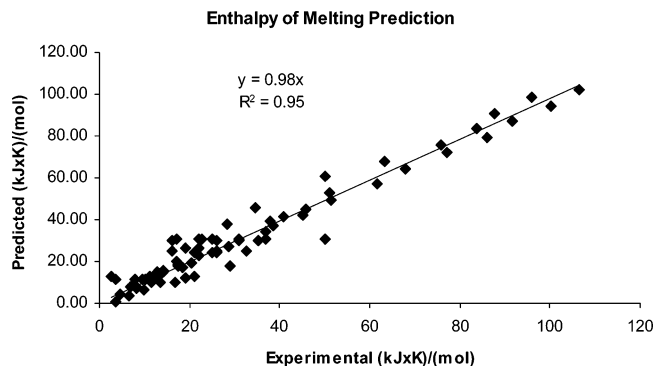
Melting point determination is very important in compound characterization.<sup>1</sup> In fact, it is the most commonly reported physical property of organic compounds. A variety of intrinsic physicochemical characteristics, including compound purity, solubility, and vapor pressure, can be predicted once the melting point is known.<sup>2</sup>

Although the melting point is akin to the boiling point, it is much more difficult to predict from a compound's structure. The largest percentage of the overall entropic change upon boiling is due to expansional entropy. Therefore, structural differences in molecules do not tend to have much effect in varying the value from Trouton's constant of 88 J/mol. By comparison, expansional entropy plays a smaller proportion of the overall entropic role in the melting process.<sup>3</sup> The major proportion of the overall entropy of fusion is due to orientational and conformational differences.<sup>4</sup> As a result, slight differences in chemical structure have a notable effect on the entropy of melting. In fact, individual values vary remarkably from the generally accepted 56 J/mol K, known as Walden's rule.<sup>5,6</sup>

As is shown in eq 1, the melting point depends on both the enthalpy ( $\Delta H_m$ ) and entropy ( $\Delta S_m$ ) of melting. These are discussed separately below.

$$T_m = \frac{\Delta H_m}{\Delta S_m} \quad (1)$$

**Enthalpy.** It is well-known that  $\Delta H_m$  can be predicted with reasonable accuracy by various group con-



**Figure 1.** Simple regression showing the calculated enthalpy of melting using an additive group contribution approach for 117 compounds. The compounds represented in the graph include all of the compounds used in the present study for which experimentally determined enthalpy values are available in the literature.

tribution schemes.<sup>7–9</sup> Figure 1 shows an example of the additive group approach of Zhao and Yalkowsky.<sup>8</sup> Each molecule is broken down into defined groups, and each group is assigned a standard enthalpic value. The sum of all these values gives a relatively accurate total enthalpy of melting. Note the high  $R^2$  value, the slope very close to 1, and the y intercept of 0. Therefore, the portion of eq 1 most in need of predictive enhancement is  $\Delta S_m$ .

**Entropy.** Although a molecular group contribution approach has been used to estimate entropy<sup>10,11</sup> as well as the melting point directly,<sup>12</sup> this method is not very accurate and cannot distinguish between isomers.<sup>1–6,8,9,13–20</sup> The large error associated with this approach can be attributed to the assumption that only the presence of specific groups in the molecule determines the entropic change. Although partially true, in many cases, a large portion of the entropy of melting is

\* To whom correspondence should be addressed. Tel.: 520-770-1259 ext 159. Fax: 520-791-2437. E-mail: jjohnson@imarx.com.

† Present address: ImaRx Therapeutics, Inc., 1636 E. 18th St., Tucson, AZ 85719.

due to the relative positions and orientations of those groups.<sup>9,20</sup> Ultimately, such variations are difficult to predict by group contribution schemes without creating a complex and less than intuitive model.

In general, an increase in entropy can be thought of as a measure of the increase in disorder of a system. In 1908, Walden reported that fusion entropies for most compounds are constant at 56 J/K mol.<sup>21</sup> This number is often referred to as Walden's rule, or Walden's constant. Walden's findings are empirical and obtained from a limited data set of coal tar derivatives, which were all relatively small and rigid.

According to Boltzmann,<sup>22</sup> eq 2 describes the molar entropy for any system from a statistical standpoint, where  $R$  is the gas constant and  $\Omega$  is the ratio of the

$$S = R \ln \Omega \quad (2)$$

number of equally probable ways a system can exist within a defined state to the number of all the possible ways available to that system. Thus,  $\Omega$  is the probability of achieving a specifically defined state. In this case, we examine the probability of achieving a melted state. Note that in the case of melting, the probability of achieving a melted state must be compared to the probability of achieving a solid state. In comparing two probabilities, it can be determined which one is more likely and how many times more likely. This comparison is

$$\Delta S_m = \int_s^l \Delta S = R \int_s^l \Delta \ln \Omega = R \ln \Omega_l - R \ln \Omega_s \quad (3)$$

Thus, the entropy of melting,  $\Delta S_m$ , is proportional to the difference between the logarithms of the probabilities,  $\ln \Omega$ , in going from the solid to the liquid state. The overall entropy measurement is commonly broken into rotational, internal, and expansional contributions.<sup>21</sup> A fourth component introduced herein is configurational entropy.

Supplementing Walden's rule with the Boltzmann definition for entropy gives eq 4:

$$T_m = \Delta H_m / C + [R \ln(\Omega_{\text{rot}} \Omega_{\text{int}} \Omega_{\text{exp}} \Omega_{\text{config}})_{\text{final}} - R \ln(\Omega_{\text{rot}} \Omega_{\text{int}} \Omega_{\text{exp}} \Omega_{\text{config}})_{\text{initial}}] \quad (4)$$

where  $C$  is Walden's constant and the rot, int, exp, and config subscripts represent the rotational, internal, expansional, and configurational components of  $\Omega$ , respectively. These are supplementary to what is described by Walden's constant. Since the final and initial states are liquid and solid, respectively, upon subtracting initial solid states from final liquid states, eq 4 becomes

$$T_m = \frac{\Delta H_m}{C + R \ln \left[ \left( \frac{\Omega_{\text{rot}}^l}{\Omega_{\text{rot}}^s} \right) \left( \frac{\Omega_{\text{int}}^l}{\Omega_{\text{int}}^s} \right) \left( \frac{\Omega_{\text{exp}}^l}{\Omega_{\text{exp}}^s} \right) \left( \frac{\Omega_{\text{config}}^l}{\Omega_{\text{config}}^s} \right) \right]} \quad (5)$$

Each  $\Omega^l$  value represents a probability in the liquid state, and each  $\Omega^s$  value represents a probability in the solid state. All of the  $\Omega$  component ratios can be replaced by their predictive parameters as follows:

$$T_m = \frac{\Delta H_m}{C + R \ln \left[ \frac{1}{\sigma} \phi \epsilon \mu \right]} \quad (6)$$

where, as depicted in Table 1,  $\sigma$ ,  $\phi$ ,  $\epsilon$ , and  $\mu$  are ratios of  $\Omega$  probabilities, based on rotational, internal, expansional, and configurational entropy as measured by symmetry, flexibility, eccentricity, and spirality, respectively. Each relationship is summarized in Table 1 and further detailed and exemplified in the following four sections.

**Rotational Symmetry ( $\sigma$ ).** The effect of molecular symmetry in determining the entropy of melting has long been recognized.<sup>18,19,23–25</sup> High symmetry reduces the entropy of melting, because the molecule has a higher probability of presenting in the correct orientation to stay in the crystal form. Another way of thinking about the role of symmetry focuses on the freedom gained upon melting. A symmetrical molecule does not have as many degrees of freedom to gain in the liquid state as does a nonsymmetrical one. Therefore, the value of  $\sigma$  can be determined by simply counting the number of ways in which a molecule can be rotated in space, resulting in the reference orientation. This is demonstrated in Figure 2.

When benzo[c]phenanthrene is used as an example, eq 7 shows how  $\sigma$  describes the rotational  $\Omega$  component ratio of eq 5.

$$\frac{1}{\sigma_{\text{benzo[c]phenanthrene}}} = \frac{\Omega_{\text{rot}}^l}{\Omega_{\text{rot}}^s} \quad (7)$$

The final and initial states of eq 7 can be further detailed by showing their respective probabilities as in eq 8.

$$\frac{1}{\sigma_{\text{benzo[c]phenanthrene}}} = \frac{\left( \frac{a_{\text{rot}}}{z_{\text{rot}}} \right)^l}{\left( \frac{b_{\text{rot}}}{z_{\text{rot}}} \right)^s} \quad (8)$$

The  $a_{\text{rot}}$  represents the number of probable molecular orientations that occur in the liquid, and  $b_{\text{rot}}$  represents the number of probable orientations that occur in the solid. Finally,  $z_{\text{rot}}$  represents the total number of molecular orientations possible. Since all possible orientations are equally probable in the liquid,  $a_{\text{rot}}$  is equal to  $z_{\text{rot}}$  and the numerator of eq 8 has a value of unity. In the solid, however, there is only one ideal orientation for nonsymmetrical molecules, which repeats in the crystal lattice. Hence,  $b_{\text{rot}}$  is equal to 1. On the other hand, when a molecule is rotationally symmetrical, the value of  $b_{\text{rot}}$  equals the number of rotations resulting in that same orientation. For every possible orientation of benzo[c]phenanthrene, there are two possible ways that particular orientation can exist, and eq 8 becomes

$$\frac{1}{\sigma_{\text{benzo[c]phenanthrene}}} = \frac{(1)^l}{\left( \frac{2}{z_{\text{rot}}} \right)^s} = \frac{z_{\text{rot}}}{2} \quad (9)$$

The value of  $z_{\text{rot}}$  is so large that it can be considered constant across all molecules; so, the amount to which rotational entropy, of any molecule, increases upon melting is directly reduced by a factor of its rotational

**Table 1. Various Types of Entropy, Their Corresponding Parameters, and Respective Measurement Techniques**

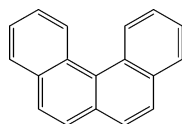
entropy parameter symbol definition	rotational rotational symmetry $\sigma$ the number of ways a rigid molecule can be rotated in space resulting in an identical orientation to a reference orientation.	internal flexibility $\phi$ the number of stable conformations possible for a flexible molecule in the liquid state.	expansional eccentricity <sup>a</sup> $\epsilon$ the ratio of the "boxed" volume around the molecule to the radius <sup>3</sup> of a sphere with the equivalent van der Waals molecular volume.	configurational spirality <sup>a</sup> $\mu$ the number of benzo[c]phenanthrene groups present in a molecule resulting in end twist due to repulsion of hydrogens.
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<sup>a</sup> Parameters that are presently introduced and examined.

**Table 2. Best Fit Equation Determined by Multiple Regression Analysis Using Only Symmetry and Flexibility as Modifiers for Walden's Rule<sup>a</sup>**

entropy of melting prediction using only $\sigma$ and $\phi$			$R^2_{\text{adj}} = 0.97$
variable	coefficient kJ/mol K	standard error kJ/mol K	P value
intercept	0.05	0.002	<0.0001
$R \ln \sigma$	-0.69	0.268	0.0114
$R \ln \phi$	1.19	0.024	<0.0001

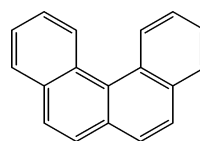
<sup>a</sup>  $N = 117$  compounds.

**Figure 2.** Benzo[c]phenanthrene. This compound has a  $\sigma$  value of 2. The molecule can be rotated horizontally  $180^\circ$  and will be in the same orientation. However, if rotated  $180^\circ$  vertically, the resulting orientation is different.

symmetry number. As defined, the rotational entropy of fusion for benzo[c]phenanthrene is 2 times less than that for a nonsymmetrical molecule.

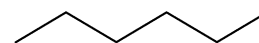
**Flexibility ( $\phi$ ).** Flexibility has been well-described in the literature as having the opposite effect from symmetry on entropic changes.<sup>1-6,8,9,13-18,26</sup> The higher the degree of flexibility a molecule possesses, the larger the entropic change upon melting. This is because a flexible molecule gains a higher degree of internal freedom when it melts as compared to a nonflexible molecule. Thus, the probability of the molecule being in the conformation necessary to form the crystal is lower for a flexible molecule than for a rigid one. The value of  $\phi$  can be calculated on the basis of the number of nonterminal single bonds in the molecule. Single bonds can rotate. They allow the molecule freedom to twist and turn in a variety of conformations. The resulting torsional angles tend to be in one of three noneclipsed positions. A Newman projection is commonly used to show there is only one way a C-C-C conformation can be anti but two equivalent ways for it to be gauche.<sup>27</sup> If these three angles were of equal energy, the probability of each torsional group being in the anti conformation would be  $1/3$  or  $0.33$ . However, the anti position is more stable because it allows each atom of the molecule to be as far away from all of its neighbors as possible. Wunderlich<sup>28</sup> showed that the probability of the anti conformation is closer to  $0.35$ . On the basis of this probability, eq 10 shows the calculation used to establish the  $\phi$  value for the flexibility of a molecule upon melting.

$$\phi = 2.85^{[\text{sp}^3 + 0.5(\text{sp}^2) + \text{RRS} - 1]} \quad (10)$$



$$\phi = 2.85^{(0 + 0.5(0) + 1 - 1)}$$

a



$$\phi = 2.85^{(4 + 0.5(0) + 0 - 1)}$$

b

**Figure 3.** Calculation of  $\phi$  for (a) benzo[c]phenanthrene and (b) hexane. For benzo[c]phenanthrene, the number of nonterminal  $\text{sp}^3$  hybridized atoms is 0, the number of noncyclic/nonterminal  $\text{sp}^2$  hybridized atoms is 0, and there is 1 rigid ring system. For hexane, the number of nonterminal  $\text{sp}^3$  hybridized atoms is 4, the number of noncyclic/nonterminal  $\text{sp}^2$  hybridized atoms is 0, and there are no rigid ring systems. Therefore,  $\phi_{\text{benzo[c]phenanthrene}}$  is 1 and  $\phi_{\text{hexane}}$  is 23.15.

The 2.85 is the reciprocal of the probability of the anti conformation, 0.35. The reciprocal represents the adjusted number of equally probable torsional angles available to each four carbon alkane series. The  $\text{sp}^3$ ,  $\text{sp}^2$ , and RRS parameters in the equation designate the number of nonterminal  $\text{sp}^3$ , nonterminal/noncyclic  $\text{sp}^2$  hybridized atoms, and rigid ring systems in the molecule, respectively. Figure 3 shows the calculations of  $\phi$  for benzo[c]phenanthrene and hexane.

Equation 11 shows how  $\phi$  describes the internal  $\Omega$  component ratio of eq 5.

$$\phi = \frac{\Omega_{\text{int}}^{\text{l}}}{\Omega_{\text{int}}^{\text{s}}} \quad (11)$$

The final and initial states of eq 11 can be further detailed by showing their respective probabilities as in eq 12, which is analogous to eq 8,

$$\phi = \frac{\left(\frac{a_{\text{int}}}{z_{\text{int}}}\right)^{\text{l}}}{\left(\frac{b_{\text{int}}}{z_{\text{int}}}\right)^{\text{s}}} \quad (12)$$

where  $a_{\text{int}}$  and  $b_{\text{int}}$  represent the number of equally probable conformations that occur in the liquid and in the solid, respectively, and  $z_{\text{int}}$  represents the total number of molecular conformations possible. In the crystal, only one conformation optimizes packing; so,  $b_{\text{int}}$  is always equal to 1. This conformation is assumed to be the one where all torsional angles are anti. The values of  $a_{\text{int}}$  and  $z_{\text{int}}$  increase identically with carbon chain length, according to eq 10, because, in the liquid, all possible conformations are equally probable. Thus, the value of  $\phi$  depends only on flexibility and, using benzo[c]phenanthrene as an example, eq 12 becomes

$$\phi_{\text{benzo[c]phenanthrene}} = \frac{\left(\frac{1_{\text{int}}}{1_{\text{int}}}\right)^l}{\left(\frac{1}{1_{\text{int}}}\right)^s} = 1 \quad (13a)$$

For comparison, the flexibility determination for hexane is

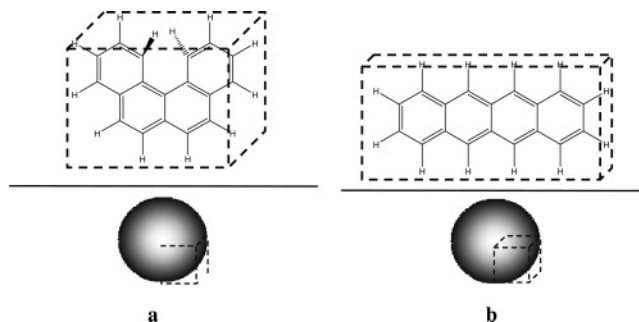
$$\phi_{\text{hexane}} = \frac{\left(\frac{23.15_{\text{int}}}{23.15_{\text{int}}}\right)^l}{\left(\frac{1}{23.15_{\text{int}}}\right)^s} = 23.15 \quad (13b)$$

Rotational symmetry and flexibility have previously been shown to improve upon Walden's prediction for flexible and small, relatively spherical molecules.<sup>1–6,8,9,13,14,16–18,26,29</sup> The need for new parameters became clear when it was consistently found that the application of this technique toward larger nonspherical rigid molecules almost invariably overestimates the melting point. For this purpose, eccentricity and spirality are introduced and evaluated as the focus of this manuscript.

## Methods

Melting points,<sup>11,32–34</sup> enthalpy of melting,<sup>11,34</sup> and geometric measurements<sup>35,36</sup> were collected from the literature for 106 hydrocarbons, including linear alkanes, cyclic alkanes, and polycyclic aromatic hydrocarbons (PAHs). These are listed in the Supporting Information. To determine the effect of the most elementary structural differences between molecules, compounds were chosen on the basis of their nonpolar and non-hydrogen-bonding nature. The group contribution approach of Zhao and Yalkowsky<sup>16</sup> was applied to estimate all enthalpy of melting values. Entropies of melting were calculated according to eq 3. Entropic components symmetry and flexibility were calculated according to the details in the previous section. The two new components, eccentricity and spirality, were also incorporated and calculated as defined below. Multiple linear regression analysis was used to determine the significance of all the proposed entropic parameters. Once significance was obtained, the coefficients of the parameters were changed to values of 1 or –1 depending upon the sign obtained in the regression equation. In addition, the intercept was assumed to be 56 J/K mol, according to Walden's rule. Thus, employing eq 1, melting points were calculated for all compounds using only the previously published parameters of rotational symmetry ( $\sigma$ ) and flexibility ( $\phi$ ) as entropic predictors. Then the two new parameters, eccentricity ( $\epsilon$ ) and spirality ( $\mu$ ), were added to investigate their potential improvement on the prediction.

**Calculation of Eccentricity and Spirality. Eccentricity ( $\epsilon$ ).** Eccentricity is meant to be a measure of how much space a freely rotating molecule requires in order to be outside the van der Waals radii of neighboring molecules. The degree to which a molecule is eccentric depends on its geometric properties and not upon the constituents present. When a rigid molecule is arranged in a manner that leaves void spaces between its moieties, those spaces may serve to enhance the crystal packing efficiency. However, in the liquid, by definition, molecules separate and are less likely to



**Figure 4.** The  $\epsilon$  values for (a) benzo[c]phenanthrene and (b) naphthacene are 10.74 and 7.9, respectively. The volume of the smallest box around benzo[c]phenanthrene is 10.74 times larger than the cubed radius of the equivalent sphere, while the volume of the smallest box around naphthacene is only 7.9 times larger.

move into each other's void spaces. The more eccentric a molecule, the farther it must move away from other molecules to evade others' void spaces and spin freely. Therefore, it can be thought of as a measure of the expansional entropy gained upon melting. Eccentricity, like flexibility, increases the entropy of melting. For example, both benzo[c]phenanthrene and naphthacene have the same number of carbons, hydrogens, and rigid rings; thus, they may consume similar volumes in the crystal. However, benzo[c]phenanthrene is considered more eccentric because of its spatial distribution. Each benzo[c]phenanthrene molecule must move further away from proximal molecules as compared to naphthacene, which does not contain void spaces because of its more linear shape. From this description, eccentricity was calculated based on eq 14.

$$\epsilon = \frac{LWT}{r^3} \quad (14)$$

The  $L$ ,  $W$ , and  $T$  represent the length, width, and thickness of the smallest box that can be formed around a rigid molecule, respectively. The  $r$  designates the radius of the equivalent sphere containing the same van der Waals volume as the molecule. Therefore, both benzo[c]phenanthrene and naphthacene are assigned the same denominator, but benzo[c]phenanthrene will require a larger box for calculation of the numerator. These dimensions are exemplified in Figure 4. According to Sanders and Wise,<sup>35</sup> the  $L$ ,  $W$ , and  $T$  dimensions of the boxes around benzo[c]phenanthrene and naphthacene are 11.9, 9.3, and 4.9 and 14.1, 7.4, and 3.9 Å, respectively. Figure 4 demonstrates these eccentricity calculations.

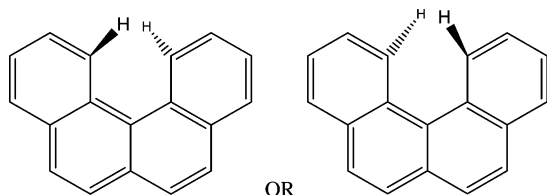
Equation 15 shows how  $\epsilon$  describes the expansional  $\Omega$  component ratio of eq 5.

$$\epsilon = \frac{\Omega_{\text{exp}}^l}{\Omega_{\text{exp}}^s} \quad (15)$$

The final and initial states of eq 15 can be further detailed by showing their respective probabilities in eq 16.

$$\epsilon = \frac{\left(\frac{a_{\text{exp}}}{z_{\text{exp}}}\right)^l}{\left(\frac{b_{\text{exp}}}{z_{\text{exp}}}\right)^s} \quad (16)$$





**Figure 5.** The  $\mu$  value for benzo[c]phenanthrene is 2 because it has one area where the proximity of the hydrogens results in an end twist of the otherwise planar molecule. The value 2 results from the fact that each such area has two possible absolute configurations.

Analogous to the previous examples, the  $a_{\text{exp}}$  represents the volume of space necessary for the molecule to move outside its neighbors' van der Waals space in the liquid. The  $b_{\text{exp}}$  represents the volume necessary for the molecule in the crystal lattice. In this case, the  $z_{\text{exp}}$  value represents the maximum space the molecule can consume as it rotates, vibrates, and spins. The values of  $a_{\text{exp}}$  and  $z_{\text{exp}}$  are equal because a molecule is assumed to utilize its maximum space when it melts. Thus, the value of  $\epsilon$  depends on how much more space the molecule occupies in the liquid compared to that in the solid. In short, the volume of the cubed radius of a sphere of equal volume to the molecule represents the volume requirement in the crystal, while the volume of the smallest box encompassing the intact molecule is intended to represent the relative increase in space requirement upon melting. When benzo[c]phenanthrene and naphthalene are used as examples, eq 16 becomes

$$\epsilon_{\text{benzo[c]phenanthrene}} = \frac{\left(\frac{10.74}{10.74}\right)^1}{\left(\frac{1}{10.74}\right)^s} = 10.74 \quad (17a)$$

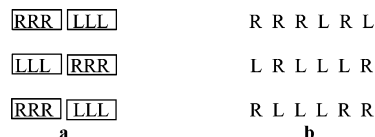
$$\epsilon_{\text{naphthalene}} = \frac{\left(\frac{7.9}{7.9}\right)^1}{\left(\frac{1}{7.9}\right)^s} = 7.9 \quad (17b)$$

**Spirality ( $\mu$ ).** Spirality is simply calculated as the number of "arcs", such as in benzo[c]phenanthrene, present on the molecule. Each semicircular area causes deviation from planarity where the proximity of the hydrogens results in marked repulsion and, consequently, a somewhat spiraled molecule. These molecular twists result in two possibilities: a right-handed spiral (RHS) and a left-handed spiral (LHS). So, part of the entropic change that occurs upon melting is due to the number of spiraled locations on the molecule, each creating two equally probable molecules. As is true for flexibility and eccentricity, spirality increases the entropy of melting. Hence, consideration of possible racemates and how they may form solid eutectics becomes important for accuracy in the entropy of fusion estimation for arced compounds. Figure 5 exemplifies the concept.

When benzo[c]phenanthrene is used as an example, eq 18 shows how  $\mu$  describes the configurational  $\Omega$  component ratio of eq 5.

$$\mu_{\text{benzo[c]phenanthrene}} = \frac{\Omega_{\text{config}}^1}{\Omega_{\text{config}}^s} \quad (18)$$

Equation 18 can be further detailed by showing the  $\Omega$



**Figure 6.** An example of right-, R, and left-handed, L, spirals and their entropic differences due to one arced area in the (a) solid and (b) liquid. Note that the R and L spiraled molecules are depicted to crystallize separately in two phases, but the liquid is shown to become a random yet homogeneous mixture of the two.

probabilities as in eq 19.

$$\mu_{\text{benzo[c]phenanthrene}} = \frac{\left(\frac{a_{\text{config}}^w}{z_{\text{config}}^w}\right)^1}{\left(\frac{b_{\text{config}}^w}{z_{\text{config}}^w}\right)^s} \quad (19)$$

The value of  $z_{\text{config}}$  is always 2 as it indicates all possible absolute configurations that can exist at one arced site. The  $a_{\text{config}}$  and  $b_{\text{config}}$  designate the number of equally likely absolute configurations (R or L) present in one homogeneous phase in the liquid and the solid, respectively. Therefore, the value for  $a_{\text{config}}$  is always 2 because the R and L spirals are equally likely to occur for any chosen location in the liquid. The value for  $b_{\text{config}}$  is always 1 because the crystal is more ordered and for any chosen location in the solid, one spiral is more likely to occur over the other. The value of  $w$  is the number of arced areas present on the molecule. If a molecule has two benzene arcs, the value of  $b_{\text{config}}^w$  becomes  $1/4$  the values of  $a_{\text{config}}^w$  and  $z_{\text{config}}^w$  because there are four different isomeric components in the mixture. In short, the value of  $\mu$  depends on how many areas of spirality are possible.

The reason  $b_{\text{config}}$  is always 1 is because the solid can be present in two possible ways. One is a mixture of separate and relatively pure R and L crystals. In this case, each crystal phase can be considered a homogeneous one-component system, as depicted in Figure 6.<sup>30,31</sup> The other is a molecular compound where R and L spirals are alternately repeated within the unit cell in a predictable manner. The assigned  $b_{\text{config}}$  value is 1 regardless of which crystal form exists and which spiral is more predominant within it. This is because both situations describe an organized distribution of R and L spirals, such that one is more probable in a chosen location over the other. Thus, in both cases, there is a large entropic gain in the liquid where the homogeneous mixture is reported to be a random mix of the two spirals at the molecular level.<sup>31</sup> Obviously, this would not be the case if the two different spirals form a complex in the liquid.

For one benzo[c]phenanthrene arc, eq 19 becomes

$$\mu_{\text{benzo[c]phenanthrene}} = \frac{\left(\frac{2^1}{2^1}\right)^1}{\left(\frac{1^1}{2^1}\right)^s} \quad (20)$$

The benzo[c]phenanthrene probability ratio of mixed

**Table 3. Best Fit Equation Determined by Multiple Regression Analysis Using Symmetry, Flexibility, Eccentricity, and Spirality as Modifiers for Walden's Rule<sup>a</sup>**

entropy of melting prediction using $\sigma$ , $\phi$ , $\epsilon$ and $\mu$			$R^2_{\text{adj}} = 0.99$
variable	coefficient kJ/mol K	standard error kJ/mol K	$P$ value
intercept	0.04	0.002	<0.0001
$R \ln \sigma$	-1.30	0.202	<0.0001
$R \ln \phi$	1.30	0.020	<0.0001
$R \ln \epsilon$	1.15	0.140	<0.0001
$R \ln \mu$	0.005	0.002	<0.0001

<sup>a</sup>  $N = 117$  compounds.

entropy for liquid over solid states is shown in eq 21.

$$\mu_{\text{benzo[c]phenanthrene}} = \frac{\Omega_{\text{config}}^{\text{l}}}{\Omega_{\text{config}}^{\text{s}}} = \frac{2}{1} = 2 \quad (21)$$

Employing eccentricity and spirality in addition to symmetry and flexibility, eq 6 is shown to improve in the melting point prediction of large aromatic compounds while still maintaining accuracy for smaller rigid, spherical, and flexible compounds.

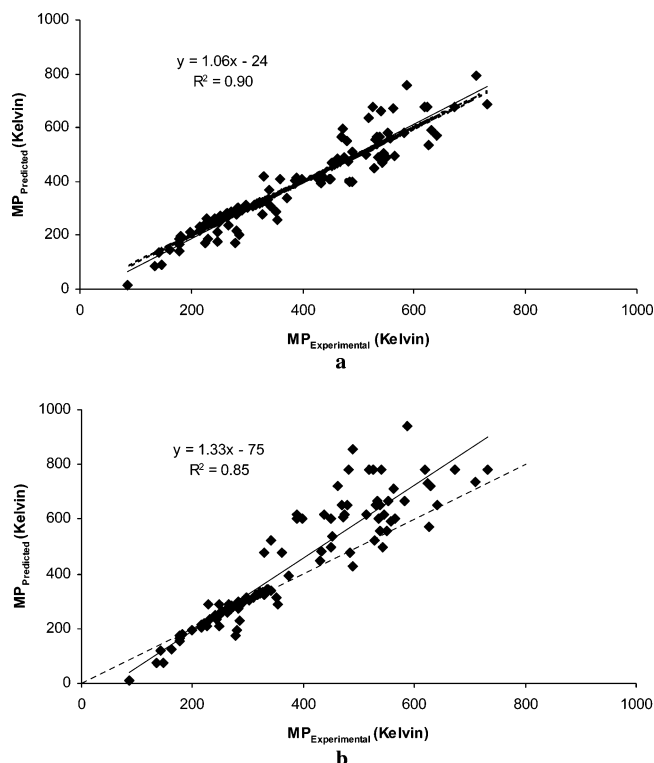
**Statistics.** Simple and multiple linear regression analyses<sup>37</sup> were carried out for confirmation of the enthalpy prediction and for both methods of entropy estimation, respectively. Correlation coefficients were calculated for all sets of the four entropic parameters to avoid correlated variables. Simple linear regression was also used to compare final melting point predictions to the experimental values. The significance of the difference between the regression line  $y$  intercept and slope of each predictive method from those of the line of identity were calculated using a comparison of the means analyses.<sup>38</sup> The average absolute error (AAE) of the prediction<sup>38</sup> was calculated for each method as follows. The absolute values of the differences between the predicted melting point values and the experimental values were calculated for each compound. These numbers were averaged to give the final AAEs.

## Results

Tables 2 and 3 show the results of multiple regression analyses to determine the coefficients, standard errors, and significance of the parameters tested for the entropy of melting. The adjusted coefficients of determination ( $R^2_{\text{adj}}$ ) are shown to allow a valid comparison of two models with different numbers of independent variables. Note that all parameters show significant improvement to the entropy of melting prediction at a  $p = 0.01$  level

**Table 4. Comparison of the  $y$  Intercepts, Slopes, Coefficients of Determination ( $R^2$ ), and Average Absolute Errors (AAE) of the Regression Lines for Both Melting Point Prediction Equations as Compared to the Experimental Melting Point Values<sup>a</sup>**

melting point equations	$y$ intercept		slope		$R^2$	AAE (K)
	coeff.	$p$ value	coeff.	$p$ value		
$T_m = \frac{\Delta H_m}{C + R \ln \left[ \frac{1}{\sigma} \phi \right]}$	-75	0.001	1.33	<0.0001	0.85	90
$T_m = \frac{\Delta H_m}{C + R \ln \left[ \frac{1}{\sigma} \phi \epsilon \mu \right]}$	-24	0.08	1.06	0.07	0.90	43

<sup>a</sup> The  $p$  values represent the significance of the difference in the coefficients from those of the line of identity.**Figure 7.** Comparison of both melting point prediction equations against the experimental values of 117 compounds using simple regression. (a) Prediction using all four entropic parameters:  $\sigma$ ,  $\phi$ ,  $\epsilon$ , and  $\mu$ . (b) Prediction using only  $\sigma$  and  $\phi$ . The solid lines are the linear regression lines, and the dotted lines are the lines of identity.

of confidence or better, and none of the correlation coefficients between variables are higher than 0.39.

Figure 7 shows the melting point prediction accuracy gained by combining the group contribution approach to predict enthalpy and using all four proposed parameters to predict entropy. The  $x$  and  $y$  axes display experimental and predicted melting points, respectively. The solid lines are the least-squares regression lines, and the dotted lines are the lines of identity. The regression<sup>37</sup> equations are shown in the top left corners of each graph. Note the slope is closer to unity, the  $y$  intercept is closer to zero, and the coefficient of determination ( $R^2$ ) is higher when all four entropic parameters are used to predict the melting point. In both graphs, the linear compounds are generally those with melting points below 400 °C. Flexibility is their only entropic component; thus, their prediction is relatively straightforward and these points are close to the regression line. The PAHs tend to have melting points above

400 °C. These compounds are more spread about the regression line because, although they are not flexible, they are likely to experience a variety of other entropic changes upon melting.

Table 4 shows the significance of the differences in predictive accuracy between the two methods. Notice that when  $\sigma$ ,  $\phi$ ,  $\epsilon$ , and  $\mu$  are used, both the slope and the intercept values do not differ significantly from the experimental values and the AAE is reduced 52% from 90 K to 43 K.

## Discussion

For the sake of identifying elementary molecular characteristics that affect the melting point, this study is restricted to alkanes, polycyclic aromatic hydrocarbons, and alkyl aromatics. Polar and hydrogen-bonding molecules would likely exhibit relatively increased intermolecular attractions (enthalpy) but decreased randomness (entropy) in the liquid state. These molecules are not considered in this study.

Figure 7 shows that eccentricity and spirality improve predictive ability. While the exclusion of the two new parameters produces a higher slope of 1.3, the regression line using all four parameters has a slope very close to 1. This is because of the presence of the large rigid compounds in the data set. Without eccentricity and spirality, the entropies of these molecules are underestimated; thus, their melting points are overestimated. Figure 7 also shows that, with the new parameters, the spread of the values about the regression line is reduced in comparison to prediction with symmetry and flexibility alone. The coefficient of determination,  $R^2$ , shown in Table 4, is significantly raised from 0.85 to 0.90. Both approaches give comparable estimations for the linear and small symmetrical compounds but are very different in their ability to predict the PAHs. An ideal model would have a  $y$  intercept of zero. Neither of the two approaches does for this data set. Although not exactly zero, the currently proposed four-parameter approach has a  $y$  intercept not significantly different at  $-24$  K in comparison to that at  $-75$  K using only symmetry and flexibility. This also reflects the improved estimation of the PAHs. As their overprediction is reduced, so is the slope of the line. Combined with the fact that the estimations of the small symmetrical and flexible molecules do not change significantly, the smaller slope, which is not significantly different from the line of identity with a slope of 1, allows the intercept of the line to more closely approach zero.

## Conclusion

Using entropic parameters of eccentricity ( $\epsilon$ ) and spirality ( $\mu$ ) in addition to rotational symmetry ( $\sigma$ ) and flexibility ( $\phi$ ) for predicting melting points of a mixture of flexible and rigid hydrocarbons provides substantial improvement in the estimation accuracy. Variations on the parameters discussed may be applicable to a much larger variety of compounds. For the 106 compounds investigated, the new parameters allowed a 52% reduction in the average absolute error of melting point prediction.

**Supporting Information Available:** Melting points, enthalpy of melting, and geometric measurements collected from the literature for 106 hydrocarbons, including linear alkanes, cyclic alkanes, and polycyclic aro-

matic hydrocarbons. This material is available free of charge via the Internet at <http://acs.pubs.org>.

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Received for review January 14, 2005  
 Revised manuscript received June 12, 2005  
 Accepted June 23, 2005

IE050055F