

## Perspective

### Perspective on the Relationship between Melting Points and Chemical Structure

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**ABSTRACT:** The importance of melting points in characterization, in the estimation of other physical properties and toxicity, and in practical applications such as ionic liquids is summarized, as are difficulties in the systematic treatment of melting points in terms of QSPR. Classical correlations of melting points of congeneric and diverse sets are discussed together with group contribution methods, combined approaches, and computer simulations.

#### Introduction

Melting point is a fundamental physical property of organic compounds, which has found wide use in chemical identification, as a criterion of purity and for the calculation of other important physicochemical properties such as vapor pressure and aqueous solubility. Despite the enormous amount of available melting point data, few useful guidelines exist for understanding the relationship between the melting point of a compound and its chemical structure. It is frequently difficult to predict whether a compound will be a solid or a liquid until it is isolated.<sup>1</sup>

The solubility of a compound in water is strongly correlated with its melting point.<sup>1</sup> An estimate of the water solubility of a compound before it is synthesized, or available in sufficient purity for analytical measurements, would be most useful. Thus, it would be helpful to be able to estimate the melting point of a compound from its chemical structure. Techniques for the estimation of the melting point of organic compounds would also significantly assist medicinal chemists in designing new drugs within a specified range of melting point and solubility. Adequate aqueous solubility is necessary for a compound to be transported to the active site within an organism.

Melting point also affects the toxicity of a compound. As noted above, melting point affects solubility, and solubility controls toxicity in that, if a compound is only

poorly soluble, its concentration in the aqueous environment may be too low for it to exert a toxic effect.<sup>2</sup>

A good overview of early work on melting point prediction is given by Lyman et al.<sup>3</sup> This perspective attempts to reflect the present position.

**Difficulties in the Correlation of the Melting Point.** The melting point is a difficult property to correlate because it is dependent upon the arrangement of the molecules in the crystal lattice as well as upon the strength of the pairwise group interactions. Available molecular descriptors do not satisfactorily describe the many-body crystal packing effects and intermolecular forces in condensed media.<sup>4</sup> Melting point is determined by the strength of a crystal lattice, which, in turn, is controlled primarily by three factors: intermolecular forces, molecular symmetry, and the conformational degrees of freedom of a molecule.<sup>2</sup>

Most inorganic ionic compounds have high melting points, because the electrostatic forces holding the ions together are extremely strong. For organic compounds, the dominant intermolecular force affecting the melting point is intermolecular hydrogen bonding. Compounds with intramolecular hydrogen bonding normally exert less intermolecular attraction and, therefore, have a lower melting point than their intermolecularly hydrogen-bonded analogues.<sup>2</sup>

Another factor that affects the melting point is the molecular motion in crystals. This can be quite significant and depends on the size and shape of the molecules, their orientation in the crystal, and on the temperature.<sup>5</sup> These motions, which can change the structure of a crystal and affect its melting point, comprise oscilla-

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tions, reorientations, and phase transitions.<sup>6</sup> Oscillations of atoms occur in all crystals and are highly temperature dependent. Reorientations include rotations of the substituents and in the molecular plane. When reorientation motions relax, rigid crystals are transformed into plastic crystals, which exhibit preliquid behavior.<sup>7</sup> When part of the translational symmetry of a crystal is lost and the rotational motions become relatively fast, the crystal reaches the liquid crystalline state. It is estimated that approximately 5–8% of all organic compounds are transformed into a liquid crystal state when close to their melting points.<sup>7</sup>

Many compounds crystallize in more than one form and hence exhibit the phenomenon of polymorphism. Polymorphism can be intriguing to the organic chemist, since it may not be clear at first whether different crystals are different compounds or just polymorphs of the same compound.<sup>8</sup>

The mechanisms of phase transitions in organic crystals are elusive. The ranges of stability for each phase are usually determined by the appearance of anomalies in the heat capacity temperature curves, but a phase transition can also be characterized by an abrupt change of optical, electrical, or mechanical properties of the sample.<sup>6</sup>

Similar problems arise in the prediction of solubility and vapor pressure of crystalline solids, as these can be regarded as a partitioning of the compound between its crystal lattice and the solvent or gas phase, respectively. If the forces holding the molecule in the crystal are strong, then the solubility and vapor pressure will be low. Conversely, the melting point will be high, as the melting point is a measure of the energy required to disrupt the crystal lattice.

Apart from the factors mentioned above, measurements of melting point are affected by the purity of a compound and experimental error.

**Literature Approaches to Correlations of Melting Point.** A variety of empirical and semiempirical methods have been used to predict melting points. These efforts have largely focused on the following:

(i) Sets of simple organic compounds that are free of dipolar and hydrogen bonding forces (e.g., hydrocarbons).

(ii) Correlations utilizing physicochemical and structural parameters, such as molecular bulkiness, cohesiveness, hydrogen-bonding parameters, and geometric factors.

(iii) Group contribution methods in which a molecular breakdown scheme is generally employed and multiple regression analysis is performed to determine the contribution of a large number of molecular fragments/groups to the melting temperature.

Such strategies obviously simplify the procedure, but they bring with them significant limitations. Group contribution methods suffer from the disadvantage that they cannot be applied to structures containing groups that are not included in the training set. Many of the physical, chemical, and structural parameters that have been used in the correlations have to be experimentally determined. These group contribution methods also do not take into account the interactions between the different groups present in a molecule and also the spatial arrangement (symmetry) of the various groups.

Finally the utilization of highly congeneric sets limits the range of applicability of the results.

We now review QSPR approaches and then group contribution methods including powerful combined approaches<sup>9</sup> and conclude with an overview of applicable molecular simulations.

**Classical QSPR Approaches to Melting Point Correlations.** The most successful predictions of melting point have been achieved for normal alkanes. A correlation of  $R^2 = 0.9980$ ,  $s = 0.51$  K was obtained for 24 compounds using topological indices such as the Wiener index and the Balaban index.<sup>10</sup>

Abramowitz and Yalkowsky<sup>1</sup> correlated the melting point of 85 rigid, non-hydrogen bonding compounds with their boiling points and symmetry numbers to study the effect of symmetry on the melting point of organic compounds. They also correlated the melting point with the boiling point, and three descriptors called SIGMAL, EXPAN, and ORTHO. SIGMAL is the logarithm of the symmetry number, EXPAN represents the cube of the eccentricity of the compound, and ORTHO depicts the number of groups that are in an ortho position to another group. In this way, an  $R$  value of 0.938 and  $s = 22.8$  (eq 1 in Table 1) was obtained.

The melting point of a series of 42 anilines was correlated by an equation including five descriptors ( $R = 0.941$ ,  $s = 24.6$  K) (eq 2 in Table 1) based on the measures of hydrogen bond donor ability ( $\alpha$ ), the hydrophobic substituent constant ( $\pi$ ), the molar refractivity (MR), the STERIMOL width parameter B2, and the indicator variable of meta-substitution ( $I_3$ ).<sup>2</sup>

Charton and Charton<sup>11</sup> studied 366 cogeneric alkanes and correlated both branched and unbranched compounds with an “intermolecular force equation” which included a variable capable of accounting for the packing energy contribution of the alkyl group. The regression equation obtained with 11 descriptors, had  $R^2 = 0.9185$ , with a standard error of 17.9 K. The contributions of the polar variables were slightly larger than those of nonpolar variables, and structural variation in the substituent was more significant than that in the alkyl group.

The melting points of 141 pyridines and piperidines were used to develop a QSPR model for these heterocycles. Six descriptors gave a reasonably good correlation of melting points with  $R^2 = 0.831$  and cross-validated  $R^2_{cv} = 0.816$ .<sup>12</sup> In continuation of this study, a similar data set (limited to pyridines only) was updated with additional data points.<sup>13</sup> A correlation of the melting points of pyridine and 140 substituted pyridines yielded a six parameter correlation with  $R^2 = 0.857$ ,  $R^2_{cv} = 0.843$ , and standard deviation  $s = 36.1$  K (eq 3 in Table 1). The most important descriptor reflected the importance of the hydrogen bonding ability of the compound. The other descriptors can be attributed to intermolecular interactions in condensed media, crystal lattice packing, and the fact that solid insulators with a smaller gap between the valence band and the unoccupied band are more resistant to disordering (melting).

A comparative study on the prediction of physical properties of aldehydes ( $n = 27$ ,  $R^2 = 0.8330$ ), amines ( $n = 48$ ,  $R^2 = 0.7950$ ) and ketones ( $n = 30$ ,  $R^2 = 0.8650$ ) using different classes of molecular descriptors (five

**Table 1. Correlation Equations (See Text for Explanation)<sup>a</sup>**

eq	no.	R <sup>2</sup>	s	temp range	ref
1 parameter equation $T_m = 0.772T_b + 110.8\text{SIGMAL} + 11.56 * \text{ORTHO} + 31.9 * \text{EXPAN} - 240.7$	1	0.9980 0.8798	0.51 22.8	178–503	10 1
$T_m = 182\alpha - 38.2\pi + 8.91\text{MR} - 62.2\text{B2} + 26.6I_3 + 329$	2	0.8855	24.6	210–462	2
11 parameter equation		0.9185	17.9		11
6 parameter equation		0.831	17.9	178–613	12
$T_m = 525.8\text{FHASA} + 14.43F_{\text{max}} + 244.7P_{\mu} - 61.61^0\text{IC} - 38.10\epsilon_{(\text{HOMO-LUMO})} + 37.02\mu_h - 61.4$	3	0.857	36.1	183–601	13
5 parameter equation		0.833 0.795 0.865			14
$T_m = 42290\text{HDSA} - 5242.5V_{\text{av},H} + 0.95\text{SM} + 419.96^1\text{SIC} - 79.2^2\text{IC} - 147.83E_{\text{max}} - 8350.41N_C + 0.004\beta + 10.63\sigma + 6738.7$	4	0.8373	30.2	185–621	15
$T_m = 61.2L_{2v} + 40.693G_{1p} + 196.34T_u - 4.843A_m - 1906.38$	5	0.8200 0.9980	21.3 1.07	290–583	16 17
four parameter equation					

<sup>a</sup>  $T_m$  = temperature of melting,  $T_b$  = boiling point temperature, FHASA = ratio of the solvent accessible area of the hydrogen bonding acceptor atoms to the total area of the molecule,  $F_{\text{max}}$  = maximum atomic force constant,  $P_{\mu}$  = maximum atomic orbital electronic population,  $^0\text{IC}$  = average information content (zero order),  $\epsilon_{(\text{HOMO-LUMO})}$  = energy gap between the HOMO and LUMO,  $\mu_h$  = total hybridization component of the molecular dipole, HDSA = hydrogen donor surface area,  $V_{\text{av},H}$  = average valency of a H atom, SM = total molecular surface area,  $^1\text{SIC}$  = average structural information content,  $^2\text{IC}$  = average information content of the order 2,  $E_{\text{max}}$  = maximum total interaction of a C–H bond,  $N_C$  = average nucleophilic reactive index for a C atom,  $\beta$  = BETA polarizability, and  $\sigma$  = symmetry number.

descriptors in each case) produced moderate correlations between the structures and the melting point.<sup>14</sup>

For the complete set of the melting points of 443 mono- and disubstituted benzenes, a correlation equation (nine descriptors,  $R^2 = 0.8373$ ,  $s = 30.19$  K) (eq 4 in Table 1) was obtained.<sup>15</sup> Six-parameter equations were used to describe each of the individual ortho-, meta-, and para-substituted benzene subsets. The importance of hydrogen bonding descriptors was again reflected in these QSPR models. Apart from the hydrogen bonding ability of the molecules, the melting point is governed by the molecular packing in crystals (effects from molecular shape, size, and symmetry), and other intermolecular interactions such as charge transfer, and dipole–dipole interactions in the solid phase.

Gramatica et al.<sup>16</sup> related the physicochemical properties of polychlorinated biphenyls (PCBs) in terms of weighted holistic invariant molecular (WHIM) descriptors. WHIM are 3D molecular descriptors that take into account the size, shape, symmetry, and atom distribution of the molecules. A four-parameter model was created from 66 WHIM descriptors for predicting the melting point (mp range 16.5–310 °C,  $n = 82$ ). The model obtained confirmed the dependence of the melting point on size variables (both directional,  $A_m$  and  $T_u$ , and nondirectional,  $L_{2v}$ ) and on symmetry variables  $G_{1p}$ . The model had an  $R^2$  value of 0.82, cross-validated  $R$  squared ( $Q^2_{\text{LOO}}$ ) = 78.5, standard deviation error in calculation (SDEC) = 21.253, and standard deviation error in predicting (SDEP) = 23.245 (eq 5 in Table 1).

The boiling point and the melting point of 15 *n*-alkanes were predicted by multiple linear regression based on the molecular structural parameters with a molecular rotation model.<sup>17</sup> The moment of inertia of the *n*-alkanes along the short axis is correlated with the boiling point with  $R = 0.9985$  and  $s = 6.97$ , but it is the moment of inertia along the long axis and the reorientation energy that are responsible for the sawtooth behavior of melting points of *n*-alkanes. A multiple regression equation with four descriptors including rotational inertia in three dimensions and reorientation energy successfully describes the melting point of *n*-alkanes (with  $R = 0.999$  and  $s = 1.07$ ).

### Group Contribution Approach to the Prediction of Melting Point.

Simamora and Yalkowsky<sup>18</sup> proposed simple group contribution methods for predicting the boiling points and melting points of rigid organic aromatics. Whereas the boiling points could be estimated by using molecular fragment values alone, melting point prediction required the aid of rotational symmetry (a nonadditive nonconstitutive property) for satisfactory estimation. They developed a melting point equation from a data set containing 1690 compounds with an error of 37.45 K for 95% statistical reliability ( $n = 1690$ ,  $R = 0.9994$ ,  $s = 17.62$ ,  $R^2 = 0.998$ ).

Jain and Yalkowsky<sup>19</sup> used the Unified Physical Property Estimation Relationship (UPPER) method to calculate 21 physical properties, including the melting point, of 405 organic compounds based strictly upon molecular structure. They found an average absolute error between observed and predicted melting points of 23 K for 338 compounds with a melting point range of 150–750 K.

A combined approach utilizing both group contribution and simple molecular geometric parameters was employed by Zhao and Yalkowsky<sup>9</sup> to predict melting points for a variety of aliphatic compounds containing various functionalities. The melting point was estimated from the ratio of the enthalpy to the entropy of melting. The enthalpy of melting is additive and constitutive and thus can be estimated from molecular group contributions. The entropy of melting, however, is neither additive nor constitutive and must be estimated by using nonadditive molecular parameters. This approach was shown to provide a simple and accurate way to predict the melting point for many commonly encountered organic compounds directly from molecular structures. The predicted versus observed melting point for 1040 aliphatic compounds was correlated. The root-mean-square error was 34.4 K for melting points, ranging from –190 to 270 °C.

**Computer Simulation of Melting Points.** Computer simulations of fluids using either the Monte Carlo (MC) or molecular dynamics (MD) method are applicable to studies of the phase transitions and related properties of compounds including the melting point.

However, most of such simulations have been carried out for simple model systems such as metals or inorganic salts. Because of the sensitivity of the results on the model potentials applied in simulations, these are presented in terms of reduced temperatures. For instance, Vladimirov et al.<sup>20</sup> have used topological descriptions of melting in a model body centered cubic (bcc) crystal. They observed that at low temperatures, the atomic displacements remained at the same average level during the whole run and the bond topological charges hardly deviated from those of a perfect lattice. At temperatures closer to the melting point, the number of elementary defects increases, defective interactions become important, and atoms of the MELT group appear. As the temperature reaches the melting point, the simulation was found to be between 0.750 and 0.775 Lennard-Jones (LJ) units.

Prior to the phase transition, the atoms in the MELT group form large connected clusters, but crystalline structure still persists over a part of the simulated ensemble. With an increase in simulation time, the solid cluster breaks into disconnected local regions which progressively decrease in size. The crystalline structure is completely lost once the temperature exceeds the melting point. Thus, melting corresponds to the breaking up of an infinite cluster formed by atoms with crystalline environment topology. In this study, computer simulations of melting in a bcc lattice used both topological description and crystalline signature for the atomic-scale visualization of the processes underlying structural modification during phase transition. The Monte Carlo approach often requires very time-consuming calculations but provides a good overview of the mechanism of melting.

The same applies to molecular dynamics simulations. For instance, Tuschiya et al.<sup>21</sup> reported the melting point of normal alkanes from molecular dynamics, using the NPT ensemble. In the NPT ensemble, the number of particles  $N$ , the pressure  $P$ , and the temperature  $T$  are fixed, and the volume will result from the system behavior. Tuschiya et al. calculated the melting point by analyzing the coordinated data obtained from the molecular dynamics calculations. They used the fact that a volume expansion occurs during the solid to liquid phase transformation and by this technique calculated the melting point of *n*-alkanes having 8–16 carbons. From the radial distribution function reflecting the arrangement of carbons, the solid–liquid-phase transformation was helpful in predicting melting points in good agreement with the measured values. The major drawback with this method is that the number of particles to be handled and computation time affects the simulation results.

Apart from normal alkanes,<sup>21–24</sup> the melting points of cyclopropane,<sup>25</sup> benzene,<sup>26</sup> and the meta- and para-isomers of anisylpinacolone<sup>27</sup> have been predicted using the molecular dynamics simulations.

Notably, molecular dynamics calculations have been successfully applied for calculations of the melting points and glass transition temperatures of polymeric nanoparticles<sup>28–30</sup> and chain polymers.<sup>31</sup> The results of such simulations predict an interesting reduction of the melting point of nanoparticles in comparison with the bulk polymer systems.

These computer simulations give considerable insight into the details of phase transition (melting) processes, but are still very time-consuming and require the intermolecular interaction potentials to be known with high precision. Therefore, various more simple physical models have been developed to predict the melting points of molecular systems.

Thus, Reynolds<sup>32</sup> used tunnel theory for calculating the melting point. According to this theory, a crystal is divided into infinite strings of molecules on a two-dimensional lattice, each string occupying a tunnel formed by neighboring strings. Molecular motion is considered only along the string direction. In a mean-field approximation, the positional correlations of a molecule with its neighbors within a string and those in different strings are separated. The resulting equations allow a smooth variation from a harmonic crystal to a tunnel model of a liquid. Approximate solutions of the equations allow the melting point to be predicted from elastic constants alone, with no adjustable parameters. Melting occurs when the crystal becomes unstable to large-amplitude transverse shear waves. The melting point–elasticity correlation is tested on 51 atomic and molecular crystals out of which 24 have melting points of approximately 4000 K. The ratio of agreement between experimental and theoretical is 0.98 ( $R = 0.98$ ). Melting point may be predicted with a standard deviation of 22% from elasticity data.

March<sup>33</sup> has linked the orientational disordering temperature, calculated from first principles, with the melting point of homonuclear diatomic molecular assemblies such as  $N_2$  and halogens. A possible extension of this approach to the theoretical prediction of melting points of polyatomics is also discussed. However, such a theoretical approval would be limited to molecules of high symmetry, e.g.,  $CH_4$ ,  $C_{60}$ .<sup>33</sup>

Ekkehard et al.<sup>34</sup> suggest that application of thermodynamic parameters for the calculation of oligonucleotide duplex stability provides the best estimates of oligonucleotide melting temperatures ( $T_m$ ). Such estimates can be used for evidence-based design of molecular biology experiments in which oligonucleotide melting behavior is a critical issue, such as temperature or denaturing gradient gel electrophoresis, Southern blotting, or hybridization probe assays on the Light Cycler. The authors developed a user-friendly program for  $T_m$  calculation of matched and mismatched probes using the Microsoft Excel and used published entropy and enthalpy values of Watson–Crick pairs, along with the salt and oligonucleotide concentrations. The 5' and 3' end stability is calculated for the estimation of primer specificity. In addition, the influence of all possible mutations under a given probe can be calculated automatically. The experimental evaluation of predicted  $T_m$  with the Light Cycler, based on 14 hybridization probes for different gene loci, showed an excellent fit between measured results and values predicted with the thermodynamic model in 14 matched, 25 single mismatched, and 8 two-point mismatched assays ( $R = 0.98$ ,  $s = 0.90$ ). This program is extremely useful for the design of oligonucleotide probes because the use of probes that do not discriminate with a reasonable  $T_m$  difference between wild-type and mutation can be avoided in advance.

## Conclusions

Melting point is a highly precise end-point, but this does not mean that its prediction is facile. In the case of melting point, the crystal lattice into which each molecule fits is different, comprising, as it does, a cage of different molecules for each compound. The melting point of a crystal is governed by the hydrogen bonding ability of the molecules, the molecular packing in crystals (effects from molecular shape, size, and symmetry), and other intermolecular interactions such as charge transfer and dipole–dipole interactions in the solid phase. Studies have shown that fairly good predictions can be made for the correlation of the melting point. However, as scales of hydrogen bonding ability are improved and better measures of shape and symmetry are obtained, improved correlations should follow. The increasing importance of ionic liquids<sup>35–37</sup> underlines the significance of understanding melting behavior.

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