

# Carnelley's Rule and the Prediction of Melting Point

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**ABSTRACT:** Carnelley (1882) made some important and useful observations on the relationship between the arrangement of the atoms in a molecule and its melting point. According to Brown and Brown (2000. *J Chem Ed* 77:724–731), Carnelley's rule states "of two or more isometric compounds, those whose atoms are the more symmetrically and the more compactly arranged melt higher than those in which the atomic arrangement is asymmetrical or in the form of long chains." Carnelley's rule can best be understood and quantitated from the dependence of the entropy of melting upon molecular geometry. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 103:2629–2634, 2014

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## INTRODUCTION

To better appreciate the roles of enthalpy and entropy in determining melting points, it is best to start with the Gibbs free energy equation:

$$\Delta G_m = \Delta H_m - T\Delta S_m \quad (1)$$

At the melting point ( $T = T_m$ ), the system is in equilibrium so that the free energy of melting is equal to 0. Therefore,

$$0 = \Delta H_m - T_m \Delta S_m \quad (2)$$

and

$$T_m = \frac{\Delta H_m}{\Delta S_m} \quad (3)$$

Thus, the melting point can be understood in terms of enthalpy and entropy.

Both the enthalpy of melting and the entropy of melting are dependent upon chemical structure. However, they are dependent in different ways. The enthalpy of melting is dependent upon the intermolecular interactions of the atoms and groups that comprise the molecule, whereas the entropy of melting is largely dependent on the arrangement of the constituent groups in the molecule. These will be discussed separately below.

## ENTHALPY OF MELTING

The enthalpy (or heat) of melting is the amount of heat required to melt 1 mol of a substance. It is equal to the difference between the pairwise attractive intermolecular interactions among the atoms and groups of the molecule in the crystal and the melt. In general, the molar heat of melting,  $\Delta H_m$ , can be described

by

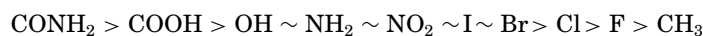
$$\Delta H_m = \sum n_i m_i \quad (4)$$

where  $n_i$  is the number of group  $i$  in the molecule and  $m_i$  is the contribution of each group  $i$  to the enthalpy of melting.

## Group Contributions to the Heat of Melting

These pairwise interactions are the result of van der Waals and hydrogen-bonding forces. They contribute to the heat of fusion in a fairly regular manner. The  $m_i$  value of a group reflects its ability to interact with groups on neighboring molecules. Hydrocarbon groups interact weakly with each other and thus have low  $m_i$  values. Dipolar groups interact more strongly and have larger  $m_i$  values, whereas hydrogen-bonding groups form the strongest intermolecular interactions and have the largest  $m_i$  values.

It is important to remember that although entropy is a determinant of the melting point, enthalpy is often the primary determinant. Table 1 lists the melting points of methyl and phenyl derivatives of some common functional groups. The general order of melting points is



In nearly all cases, the methyl substituted compounds melt lowest. The methyl compounds are followed by the dipolar halogens in roughly the order of their size, and the nitro compounds. The weakly hydrogen-bonding hydroxyl and amino groups tend to have comparable melting points, whereas carboxylic acids and amides, which are larger and can form reinforced hydrogen bonds, consistently have the highest melting points.

The data in Table 1 and Figure 1 show that there is a rank-order correlation between the melting points of aliphatic and aromatic groups. That same data show that there are significant differences between the contributions of the same substituent on aliphatic and aromatic compounds.

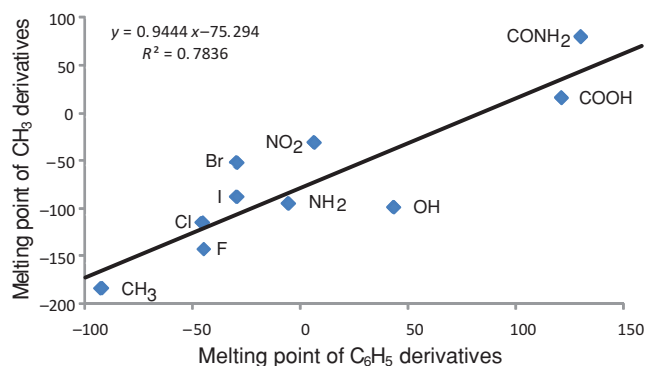
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**Table 1.** Melting Points of Toluene and Ethane Homomorphs

Aromatic	MP	Difference	Aliphatic	MP	Difference
Toluene	-93	0	Ethane	-183	0
Fluorobenzene	-40	43	Fluoromethane	-142	41
Chlorobenzene	-46	47	Chloromethane	-114	69
Bromobenzene	-30	63	Bromomethane	-87	96
Iodobenzene	-30	63	Iodoethane	-51	132
Nitrobenzene	6	99	Nitromethane	-30	153
Phenol	43	136	Methanol	-98	85
Aniline	-6	87	Methylamine	-94	89
Benzoic acid	121	214	Acetic acid	17	200
Benzamide	130	223	Acetamide	81	264

**Figure 1.** Relationship between the melting points of CH<sub>3</sub>-G and C<sub>6</sub>H<sub>5</sub>-G for selected groups.

## ENTROPY OF MELTING

The entropy of melting is defined as the difference between the entropy of the crystal and the liquid at the melting point, that is,

$$\Delta S_m = \Delta S^c - \Delta S^l \quad (5)$$

The molar entropy of a crystal phase is related to its probability of existence by

$$S^c = -R \ln \Omega^c \quad (6)$$

where  $\Omega^c$  is the number of ways in which 1 mol of material can exist within the confines of a crystal.

We often describe  $\Delta S^c$  as being related to the probability of a collection of molecules conforming to the crystal as

$$\Delta S^c = -R \ln \left( \frac{\Omega^c}{\Omega^{\text{not } c} + \Omega^c} \right) \quad (7)$$

The entropy change associated with any process is related to the relative probabilities of the existence of the final and initial states. For the process of melting, we can write the Boltzmann relationship as

$$\Delta S_m = -R \ln \rho_m \quad (8)$$

where

$$\rho_m = \left( \frac{\Omega^c / (\Omega^l + \Omega^c)}{\Omega^l / (\Omega^l + \Omega^c)} \right) = \left( \frac{\Omega^c}{\Omega^l} \right) \quad (9)$$

and where  $\Omega^l$  is the number of ways that 1 mol of material can be found that would constitute the liquid phase, and  $\Omega^c$  is the much smaller number of ways that those molecules can exist as a crystal. The probability ratio for melting,  $\rho_m$ , is therefore the ratio of the probability of finding 1 mol ( $6.02 \times 10^{23}$  molecules) of substance in the crystal to finding the same number of molecules within the confines of the liquid phase. Note that  $\rho$  is a ratio of two probabilities, but it is not itself a probability.

## Factors Affecting the Entropy of Melting

The probability ratio for melting can be expanded into the product of its rotational, expansional, and conformational components.

$$P_m = w \times P_m^{\text{rot}} \times P_m^{\text{conf}} \times P_m^{\text{expan}} \quad (10)$$

where  $w$  is a constant that is related to the restrictions of the crystal lattice substitution of entropies for probability ratios via the Boltzmann relationship in (Eq. (8)) allows the entropy of melting to be expressed as the sum of translational, rotational, and conformational components.

$$\Delta S_m = W + \Delta S_m^{\text{rot}} + \Delta S_m^{\text{conf}} + \Delta S_m^{\text{expan}} \quad (11)$$

where  $W = -R \cdot \ln w$

## Constant

Walden's rule is the most well-known generalization of the entropy of melting for organic compounds. Walden<sup>1</sup> observed that the entropy of melting of a selection of coal tar derivatives tended to average near 57 J/K mol. By analogy to Trouton's rule, this value is largely because of the increase in translational freedom that accompanies melting. However, because the crystal lattice places far more restrictions on molecular motion than the liquid, the entropy of melting is far less constant than the entropy of boiling. The deviation of the entropy of melting from Walden's rule can be related to molecular geometry. The structural dependency of the rotational, conformational, and expansional entropies of melting is responsible for the success of Carnelley's rule. In fact, Carnelley's rule, although directed to melting points, is a reflection of the deviation of the entropy of melting from Walden's rule. The structural parameters that characterize the above components are symmetry, flexibility, and eccentricity. These will be discussed separately below. Note that the use of additional parameters will modify the value of the constant in Eq. (10).

## Symmetry

Carnelley<sup>2</sup> was the first to observe the relationship between molecular symmetry and melting point. Carnelley's rule, which was thoroughly reviewed by Brown and Brown,<sup>3</sup> states that the most symmetrical of a group of isomers will have the highest melting point. Increasing the rotational symmetry of a molecule

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