

# Effect of molecular symmetry on melting temperature and solubility

Rodolfo Pinal

Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN, 47907, USA. E-mail: rpinal@purdue.edu; Fax: +1 765 494 6545; Tel: +1 765 496 6247

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Molecular symmetry has a pronounced effect on the melting properties and solubility of organic compounds. As a general rule, symmetrical molecules in crystalline form have higher melting temperatures and exhibit lower solubilities compared with molecules of similar structure but with lower symmetry. Symmetry in a molecule imparts a positive amount of residual entropy in the solid phase (*i.e.*, more possible arrangements leading to the same structure). This means that the entropy of a crystal of symmetric molecules is greater than the entropy of crystal of a similar, but non-symmetric molecule. An analysis is presented relating the enthalpy, entropy and temperature of melting for an idealised system of structural isomers of different molecular symmetries. The analysis presented helps explain why often, yet not always, the crystal of a more symmetric molecule, which has greater entropy to start (closer to that of the liquid), also exhibits a greater gain in entropy upon melting, compared with the crystal of a less symmetrical molecule. The residual entropy due to molecular symmetry has the direct effect of reducing the entropy gain upon melting (a negative effect). However, molecular symmetry also exerts indirect effects on both the entropy and enthalpy of melting. These indirect effects, imposed by the condition of equilibrium melting, are positive, such that it is the balance between the direct and indirect effects what determines the value observed for the entropy of melting of the symmetric molecules. When the indirect effect of molecular symmetry is greater than its direct effect, the observed entropy gain upon melting of the more symmetrical molecule is greater than that of a less symmetrical one.

Chemists know that molecular symmetry has a pronounced effect on the melting temperature and solubility of organic compounds.<sup>1</sup> As a general rule (Brown and Brown<sup>2</sup> have proposed calling it Carnelley's rule), crystals of symmetrical molecules have higher melting temperatures and are less soluble than the crystals of less symmetrical molecules with similar structures.<sup>1,2</sup> The relationship between melting temperature and solubility has been established, in a definite way, by Yalkowsky and Valvani.<sup>3</sup> In fact, symmetrical molecules are less soluble precisely because of the higher melting temperature of their crystals.<sup>4</sup> The intimate connection is thus between molecular symmetry and melting temperature. Melting temperature is a peculiar property of materials; it is in many respects a bulk property, but has the special characteristic of strongly reflecting the rather subtle molecular feature of symmetry.<sup>5</sup> Gavezzotti<sup>1</sup> concluded that the effect of molecular symmetry on melting is a true solid state effect, and that the few exceptions to the general rule of symmetrical molecules exhibiting higher melting temperature, can be explained. Among the exceptions to the general rule is the fact that *ortho*-disubstituted benzene derivatives in some instances have higher melting temperature than the more symmetrical *para*-isomers. In addition, despite the fact that *ortho*- and *meta*-isomers have the same symmetry, it is also common for *ortho*-isomers to have higher melting temperature than their *meta*-counterparts. The type of molecular arrangements that *ortho*-disubstituted benzenes can adopt in the crystal phase has been discussed to explain their higher melting temperature over their *para* or *meta* counterparts.<sup>1</sup> Exceptions to the above mentioned general rule are also encountered for some, but not all, hydrogen bonding compounds. In this case, the structure-defining character of hydrogen bonding is certainly capable of overriding subtler shape effects such as symmetry.<sup>1</sup>

A simple explanation for a high melting temperature is often given in terms of the relationship between the enthalpy ( $\Delta H_m$ ), entropy ( $\Delta S_m$ ) and temperature ( $T_m$ ) of melting. Since high values of  $T_m$  are favoured by high values of  $\Delta H_m$  and low values of  $\Delta S_m$ .<sup>6</sup>

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

A high enthalpy of melting implies large bonding energies,<sup>6</sup> and molecular symmetry may contribute to stronger crystal packing *via* shape-cohesion effects.<sup>1</sup> The effect of molecular symmetry on the entropy of melting is quantifiably more direct. Yalkowsky *et al.*<sup>7</sup> and Dannenfelser and Yalkowsky<sup>8</sup> have accounted for the effect of molecular symmetry on the entropy of melting by including the symmetry number ( $\sigma$ ). In the solid phase, the symmetry of a molecule results in a residual amount of molar entropy of magnitude  $R \ln \sigma$  above that of a similar but non-symmetrical molecule. Consequently, the difference in entropy between the liquid and solid phases will be smaller for the more symmetrical molecule. This in turn means that symmetry in a molecule has the effect of reducing the entropy gained upon melting for that compound ( $\Delta S_m$ ). Either of the two effects listed above, not to mention a combination of the two, would result in a higher melting temperature for a symmetrical molecule over a non-symmetrical one.

The great intuitive appeal of the explanation given above comes from the fact that its conceptual and numerical arguments are not only valid, but entirely consistent. However, the same account fails to explain a very common observation, namely, the fact that symmetrical molecules, which as a general rule do have higher melting temperatures, quite often have also greater entropies of melting than their less symmetrical isomers. Table 1 gives a list of pairs of structural isomers with different molecular symmetry. In all examples listed, the more symmetrical isomer has the higher melting temperature. However, in all cases too, the higher melting isomer has also the higher entropy of melting. It should be pointed out that a more symmetrical isomer exhibiting both higher temperature and entropy of melting is not at all an uncommon occurrence, as exemplified in Table 1. Given that the explanation for a higher melting temperature given after eqn. (1) is a valid one, it becomes clear that, in addition to the term  $R \ln \sigma$ , another factor of common occurrence must be part of the interplay between molecular symmetry and the observed entropy of melting. The validity of eqn. (1) also means that in every case in which the more symmetrical isomer exhibits both a higher temperature and a higher entropy of melting, its enthalpy of melting must also be greater than that of the less symmetrical isomer. It follows that the effect of molecular symmetry on melting

**Table 1** Temperature, entropy and enthalpy of melting for pairs of structural isomers with different molecular symmetry

Compound	$\sigma$	Less symmetrical			More symmetrical			$\sigma$	Compound
		$\Delta H_m^{\circ}/\text{kJ mol}^{-1}$	$T_m/\text{K}$	$\Delta S_m^{\circ}/\text{J mol}^{-1}\text{ K}^{-1}$	$\Delta S_m^{\circ}/\text{J mol}^{-1}\text{ K}^{-1}$	$T_m/\text{K}$	$\Delta H_m^{\circ}/\text{kJ mol}^{-1}$		
Phenanthrene	2	16.46	372.3 <sup>a</sup>	44.21 <sup>a</sup>	60.11 <sup>a</sup>	488.9 <sup>a</sup>	29.39	4	Anthracene
Benz[e]pyrene	2	17.34	454.5 <sup>a</sup>	38.15 <sup>a</sup>	57.89 <sup>a</sup>	550.9 <sup>a</sup>	31.89	4	Perylene
<i>o</i> -Dibromobenzene	2	13.84	280.2 <sup>b</sup>	49.4 <sup>c</sup>	57 <sup>c</sup>	360.4 <sup>b</sup>	20.54	4	<i>p</i> -Dibromobenzene
<i>m</i> -Dichlorobenzene	2	12.56	248.3 <sup>d</sup>	50.6 <sup>c</sup>	61.1 <sup>c</sup>	326.1 <sup>d</sup>	19.92	4	<i>p</i> -Dichlorobenzene
1,2,3,5-Tetramethylbenzene	2	12.97	249.4 <sup>d</sup>	52 <sup>c</sup>	59.3 <sup>d</sup>	352.3 <sup>d</sup>	20.89	4	1,2,4,5-Tetramethylbenzene
<i>m</i> -Xylene	2	11.55	225.2 <sup>d</sup>	51.3 <sup>d</sup>	59.7 <sup>c</sup>	286.3 <sup>e</sup>	17.09	4	<i>p</i> -Xylene
<i>o</i> -Xylene	2	13.60	247.8 <sup>c</sup>	54.9 <sup>e</sup>	59.7 <sup>c</sup>	286.3 <sup>e</sup>	17.09	4	<i>p</i> -Xylene

<sup>a</sup>Ref. 17. <sup>b</sup>Ref. 18. <sup>c</sup>Ref. 8. <sup>d</sup>Ref. 4. <sup>e</sup>Ref. 19. <sup>f</sup>Ref. 20. <sup>f</sup>Given as  $T_m \Delta S_m$ .

should be expected to have explicit components on both the entropy and enthalpy of melting. An analysis of the effect of molecular symmetry on the corresponding melting parameters is presented in the following section. The system chosen for such analysis involves a set of idealised isomers of different molecular symmetry, such that the difference in their symmetry is the main variable responsible for the observable differences between the melting properties of the two isomers.

### Effect of molecular symmetry

Consider the hypothetical case of two isomeric molecules, **1** and **2**. The two molecular species make up a system that will be here referred to as ideal isomers, such that the only difference between the two is their symmetry. The symmetry number  $\sigma$ , will be used as symmetry descriptor in the present discussion. The symmetry number used here is the same as that used by Yalkowsky *et al.*<sup>7</sup> for estimating the entropy of melting. The symmetry number of a molecule is the number of indistinguishable positions in space that a molecule can have by rigid rotations. This is also the number used in the calculation of the rotational partition function.<sup>13</sup> The benzene molecule for example, which belongs to symmetry group  $D_{6h}$ , has  $\sigma = 12$ . This means that a molecule of benzene can be rotated to give 12 undistinguishable orientations: it can be rotated by 60° six times, either clockwise or counterclockwise, giving six indistinguishable orientations. Since the molecule is flat, six more indistinguishable orientations are obtained by repeating the above operation after flipping the molecule such that its back side faces front.

Consider that the molecules of the two ideal isomers in question are similar enough in all other respects such that their bulk properties, as would be the case for the heat capacities of their corresponding crystal and liquid states are very nearly the same. In this idealised case, the heat capacities of solids **1** and **2** are nearly equal, as well as the heat capacities of the two corresponding liquids. The two molecules can be expected to have different melting temperatures but similar boiling points,<sup>5,7</sup> thus:

$$\sigma_1 \neq \sigma_2 \quad (2a)$$

$$C_{p1}^s \approx C_{p2}^s = Cp^s \quad (2b)$$

$$C_{p1}^L \approx C_{p2}^L = Cp^L \quad (2c)$$

where  $C_p$  is the heat capacity, the subscripts 1 and 2 denote molecular species **1** and **2**, respectively, and the superscripts s and L, denote solid and liquid phase, respectively. For purposes of simplicity, consider that  $\sigma_2 > \sigma_1$  and  $\sigma = 1$ . The particular choice of  $\sigma$  values does not alter the results but greatly simplifies the presentation.

The symmetry of a molecule gives it  $\sigma$  indistinguishable positions; the same statement can be made in terms of the residual entropy,  $S_r$ , that symmetry confers to the molecule, so that for one mole:<sup>7,8</sup>

$$S_r = R \ln \sigma \quad (3)$$

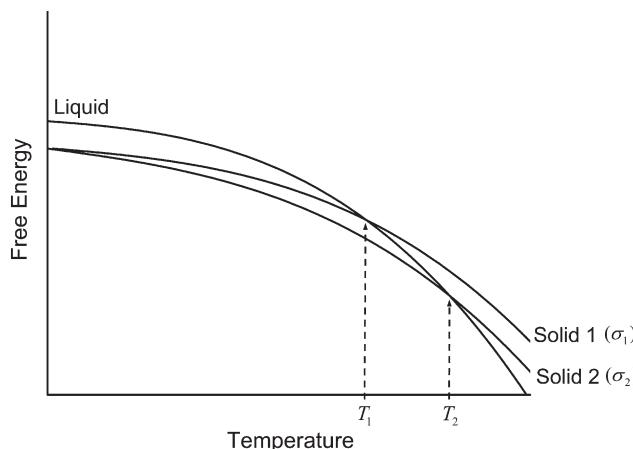
where  $R$  is the gas constant. Thus, for two molecules of different symmetry, the more symmetric one will have an amount of residual molar entropy, relative to the less symmetric molecule, of the following magnitude:

$$S_r^2 = R \ln \left( \frac{\sigma_2}{\sigma_1} \right) \quad (4)$$

For the system under consideration here, since  $\sigma_1 = 1$ , molecular species **1** will carry zero residual entropy, whereas molecular species **2** will carry an amount of residual entropy,  $S_r^2 = R \ln \sigma_2$ . This residual entropy, being purely configurational, is independent of temperature, and should persist as absolute zero is approached, such that the entropies of the two solids are related by:

$$S_2^s(T) = S_1^s(T) + R \ln \sigma_2 \quad (5)$$

It is also pertinent to point out that any effect of the residual entropy of species **2** is entirely consistent with the assumptions formulated as eqns. (2a) and (2b). Since the term  $R \ln \sigma_2$  is constant, it will have a direct effect on both the magnitude and slope, but not on the curvature (*i.e.*, on  $C_{p2}^s$ ), of the free energy of species **2**, as a function of temperature. Fig. 1 provides a graphical representation of the effect that the residual entropy has on the Gibbs free energy ( $G$ ) of molecular species **1** and **2** in the solid state in relation to that of the liquid. The points  $T_1$  and  $T_2$  in the figure correspond to the melting temperatures of isomers **1** and **2**, respectively. These are the two temperature values, one for each isomer, at which solid and liquid have the same free energy. At any given temperature  $T$ , the more symmetrical species **2** will have a negative excess (a deficit) in molar free energy equal to  $-RT \ln \sigma_2$ , relative to species **1**. This deficit in free energy becomes zero at absolute zero and increases linearly with temperature, such that when species **1** melts at  $T_1$ , the crystal of species **2** has a free energy that is precisely  $RT_1 \ln \sigma_2$  lower than that of the liquid. This means that at  $T_1$ , the solid of species **2** is still thermodynamically more stable than the liquid. Consequently, species **2** will not melt until a higher temperature,  $T_2$ , where the free energy of its solid is the same as that of the liquid, as shown in Fig. 1.



**Fig. 1** Effect of molecular symmetry on melting temperature. Free energy as a function of temperature for the solids of two isomers with different symmetry ( $\sigma$ ) and the liquid phase. At any given temperature below the melt, the difference between the line for solid species **1** and solid species **2**, is  $RT \ln (\sigma_2/\sigma_1)$ . The less-symmetrical species **1** has a melting temperature  $T_1$ , the more-symmetrical species **2** will not melt until its solid line intersects the liquid line at  $T_2$ .

The above considerations can be alternatively expressed as follows. In order for the melting of species **1** to take place, the following condition is necessary:

$$G^L(T_1) = G_1^s(T_1) \quad (6)$$

since the same criterion applies to the melting of the other isomer, species **2** will not melt until it reaches a temperature,  $T_2$ , where the free energy of its solid phase is the same as that of the liquid, *i.e.*, when

$$G^L(T_2) = G_2^s(T_2) \quad (7)$$

Eqns. (6) and (7) describe the solid–liquid crossing points, one for each isomer, shown in Fig. 1. The figure can be interpreted as depicting the change in melting temperature brought about by a hypothetical change in molecular symmetry. The effect of molecular symmetry is to produce changes in melting temperature (*i.e.*, from  $T_1$  to  $T_2$ ) that can be, and frequently are, quite significant. It is important to bear in mind (as stated above) that even though the residual entropy due to the symmetry of a molecule has a constant (temperature independent) value, its effect on free energy increases in direct proportion with temperature. This fact has important ramifications. As discussed below, it is precisely because of its relationship with free energy, that the constant residual entropy

term,  $R \ln \sigma$ , has both a direct and an indirect effect on the magnitude of the entropy of melting. Another characteristic of the type of system considered here is that the enthalpy and entropy of melting at  $T_2(\sigma_2)$  cannot be arbitrarily independent of the corresponding quantities at  $T_1(\sigma_1)$ .

First consider that for the liquid of species **1** at  $T_1$ :

$$H^L(T_1) = H_1^s(T_1) + \Delta H_{m1} \quad (8)$$

where  $H$  denotes enthalpy and  $\Delta H_{m1}$  is the enthalpy change upon melting for species **1**, and the super- and sub- scripts are the same as above. In a similar fashion we have that for the entropy of species **1** at  $T_1$ :

$$S^L(T_1) = S_1^s(T_1) + \Delta S_{m1} \quad (9)$$

where  $S$  denotes entropy and  $\Delta S_{m1}$  is the entropy of melting of species **1**. For the solid of species **2** at  $T_2$  we have:

$$H_2^s(T_2) = H_1^s(T_1) + \int_{T_1}^{T_2} C_p^s dT \quad (10)$$

where the first term on the right hand side is the result of applying eqn. (2b), *i.e.*, it corresponds to the third law enthalpy. It should be pointed out that in addition to eqn. (2b), eqn. (10) also bears the implicit assumption that the zero point energy of ideal isomers is the same, thus making  $H_2^s(T) = H_1^s(T)$ , which corresponds to the enthalpy counterpart of eqn. (5). Further discussion on the use of third law enthalpies and entropies will be provided later.

In an analogous manner, we have that for the entropy of the solid of species **2** at  $T_2$ :

$$S_2^s(T_2) = S_1^s(T_1) + R \ln \sigma_2 + \int_{T_1}^{T_2} \frac{C_p^s}{T} dT \quad (11)$$

Making use of eqn. (8), we have that for the enthalpy of the liquid at  $T_2$ :

$$H^L(T_2) = H_1^s(T_1) + \Delta H_{m1} + \int_{T_1}^{T_2} C_p^L dT \quad (12)$$

and applying eqn. (9) we have that for the entropy of the liquid:

$$S^L(T_2) = S_1^s(T_1) + \Delta S_{m1} + \int_{T_1}^{T_2} \frac{C_p^L}{T} dT \quad (13)$$

We are interested in finding the magnitude of the enthalpy and entropy of melting of the (more) symmetrical species,  $\Delta H_{m2}$  and  $\Delta S_{m2}$ , measured at  $T_2$ , in relation to the corresponding quantities  $\Delta H_{m1}$  and  $\Delta S_{m1}$ , measured at  $T_1$ , for the less symmetrical isomer. Subtracting eqn. (10) from eqn. (12) we get:

$$\Delta H_{m2} = \Delta H_{m1} + \int_{T_1}^{T_2} \Delta C_p dT \quad (14)$$

where the term  $\Delta C_p = C_p^L - C_p^s$  corresponds to the difference in heat capacity between the liquid and solid phases. In order to find the entropy of melting for the (more) symmetrical molecular species, we subtract eqn. (11) from eqn. (13) and obtain:

$$\Delta S_{m2} = \Delta S_{m1} - R \ln \sigma_2 + \int_{T_1}^{T_2} \frac{\Delta C_p}{T} dT \quad (15)$$

Eqns. (14) and (15) show the quantitative effect of molecular symmetry on the enthalpy and entropy of melting, respectively. Note that in cases where the molecular species under consideration have both symmetry numbers greater than unity, eqn. (15) still applies. In such cases, the second term on the right hand side of eqn. (15) would originate from eqn. (4).

By looking at the last two expressions above, it becomes apparent that even though molecular symmetry has an effect on both the enthalpy and entropy of melting, the nature or direction of the effect is not the same for the two quantities. The second term on the right hand side of eqn. (14) is positive, hence the enthalpy of melting of the more symmetric species will be greater than that of the less symmetrical one. In contrast, for the entropy of melting, the effect of molecular symmetry comes in the form of two counteracting effects as seen in eqn. (15). Increased molecular symmetry has a direct negative effect on the entropy of melting represented by the term  $-R \ln \sigma_2$ . This term has already been introduced for the prediction of entropy of melting by Yalkowsky *et al.*<sup>7</sup> and by Dannenfelser and Yalkowsky.<sup>8</sup> The last term in eqn. (15) carries an indirect and positive effect of molecular symmetry on the entropy of melting. This particular term is imposed by the condition of equilibrium melting. Since the last two terms on the right hand side of eqn. (15) have opposite signs, the magnitude of  $\Delta S_{m2}$  could move in either direction of  $\Delta S_{m1}$ , depending on the balance between the (indirect) positive and (direct) negative effects. Gavezzotti<sup>1</sup> has found that the effect of molecular symmetry on melting is one of an essentially enthalpic nature. Based on eqns. (14) and (15), a similar assessment can be made by stating that the enthalpic effect is always present in the same (positive) direction, whereas the entropic one, which can go in either (positive or negative) direction, may or may not be observed, depending on the case. This explains why in some cases the entropy of melting of the more symmetrical molecule is greater than that of the less symmetrical one, whereas in other cases the opposite is true.<sup>9</sup>

### Effect of molecular symmetry on solubility

The expression for the ideal solubility of crystalline substances is given by:<sup>4</sup>

$$\ln X_1 = -\frac{\Delta S_{m1}(T_1 - T)}{RT} + \frac{1}{RT} \int_T^{T_1} \Delta C_p dT - \frac{1}{R} \int_T^{T_1} \frac{\Delta C_p}{T} dT \quad (16)$$

where  $X_1$  is the ideal mole fraction solubility of species **1** and  $T$  is the absolute temperature of the measurement. The ideal solubility is a property of the solute alone, *i.e.*, completely independent of the solvent, and represents the parameter of choice for investigating the limit that molecular symmetry can have on solubility. Eqn. (16) is a general expression that applies to any crystalline substance, thus for species **2**:

$$\ln X_2 = -\frac{\Delta S_{m2}(T_2 - T)}{RT} + \frac{1}{RT} \int_T^{T_2} \Delta C_p dT - \frac{1}{R} \int_T^{T_2} \frac{\Delta C_p}{T} dT \quad (17)$$

The difference between eqns. (16) and (17) is therefore a measure of the effect of molecular symmetry on solubility. Substituting eqn. (15) into eqn. (17), followed in turn by subtraction of the resulting expression from eqn. (16), after some rearrangement gives:

$$\begin{aligned} \ln \frac{X_1}{X_2} = & -\frac{\Delta S_{m1}(T_2 - T_1)}{RT} + \frac{(T_2 - T)}{T} \ln \sigma_2 - \\ & \frac{1}{RT} \int_{T_1}^{T_2} \Delta C_p dT + \frac{T_2}{RT} \int_{T_1}^{T_2} \frac{\Delta C_p}{T} dT \end{aligned} \quad (18)$$

Since eqn. (18) results from the difference of two ideal solubility expressions, it is not surprising that the expression is very similar in form. Note that the second term on the right hand side of eqn. (18), which corresponds to the direct contribution of molecular symmetry on solubility, has the effect of increasing the ratio of solubilities and has a multiplying term that is always positive. The effect of molecular symmetry on solubility is, in addition, more than proportional, since  $T_2$  will increase with an increase in  $\sigma_2$ . The first

two terms on the right hand side of eqn. (18) can be expected to be the most significant ones. It is common practice in ideal solubility calculations to neglect the terms involving the  $\Delta C_p$  term. This term is often considered small compared to the entropy of melting. In addition, the two terms involving  $\Delta C_p$  in eqns. (16) and (17) tend to cancel each other, since they appear with opposite signs. This type of simplification is generally accepted as one that introduces small errors.<sup>4</sup> However, it is important to point out that, as discussed below, the heat capacity terms cannot be as readily neglected when relating the enthalpy or entropy of melting of one ideal isomer to another.

### Relationship between the melting temperatures

Eqns. (14) and (15) relate the enthalpies and entropies of melting, respectively, for two structural isomers with different symmetry. In order to find the relationship between the two melting temperatures, consider the following relationships:

$$\Delta H_{m2} = T_2 \Delta S_{m2} \quad (19a)$$

$$\Delta H_{m1} = T_1 \Delta S_{m1} \quad (19b)$$

substituting eqns. (14) and (15) on the left and right hand sides, respectively, of eqn. (19a), followed in turn by substitution of eqn. (19b) into the resulting expression, after some rearrangement gives:

$$\int_{T_1}^{T_2} \Delta C_p dT - T_2 \int_{T_1}^{T_2} \frac{\Delta C_p}{T} dT = \Delta S_{m1}(T_2 - T_1) - RT_2 \ln \sigma_2 \quad (20)$$

There is no simple analytical solution for either temperature in the equation above. This is true even if the term  $\Delta C_p$  were to be treated as a constant independent of temperature, which it is not. However, something of significance becomes immediately apparent from eqn. (20), namely, the fact that the overall magnitude of the effect of molecular symmetry on melting temperature is of the same magnitude as the combined contribution of the  $\Delta C_p$  terms. If the magnitude of  $\Delta C_p$  is assumed negligibly small in eqn. (20), the result

$$\Delta S_{m1}(T_2 - T_1) = RT_2 \ln \sigma_2 \quad (21)$$

which has a simple solution for either temperature, can be readily shown to correspond, exactly, to the expression used by Wei.<sup>5</sup> However, it should be pointed out that Wei's expression was derived from the explicit assumptions:

$$\Delta H_{m2} = \Delta H_{m1} \quad (22a)$$

and

$$\Delta S_{m2} = \Delta S_{m1} - R \ln \sigma_2 \quad (22b)$$

Therefore, although it is possible for eqn. (20) to equal zero, the result (eqn. (21)) is effectively restricted to a very specific set of mutually consistent values for the enthalpy and entropy of melting. Neglecting the  $\Delta C_p$  term as negligibly small corresponds to doing the same thing to the overall effect of molecular symmetry on melting for a vast number of instances, *i.e.*, it corresponds to excluding all systems where  $\Delta H_{m2} > \Delta H_{m1}$  and/or  $\Delta S_{m2} \geq \Delta S_{m1}$ . There is no *a priori* reason for simplifying eqn. (20) by assigning a negligibly small magnitude to  $\Delta C_p$ .

### Discussion

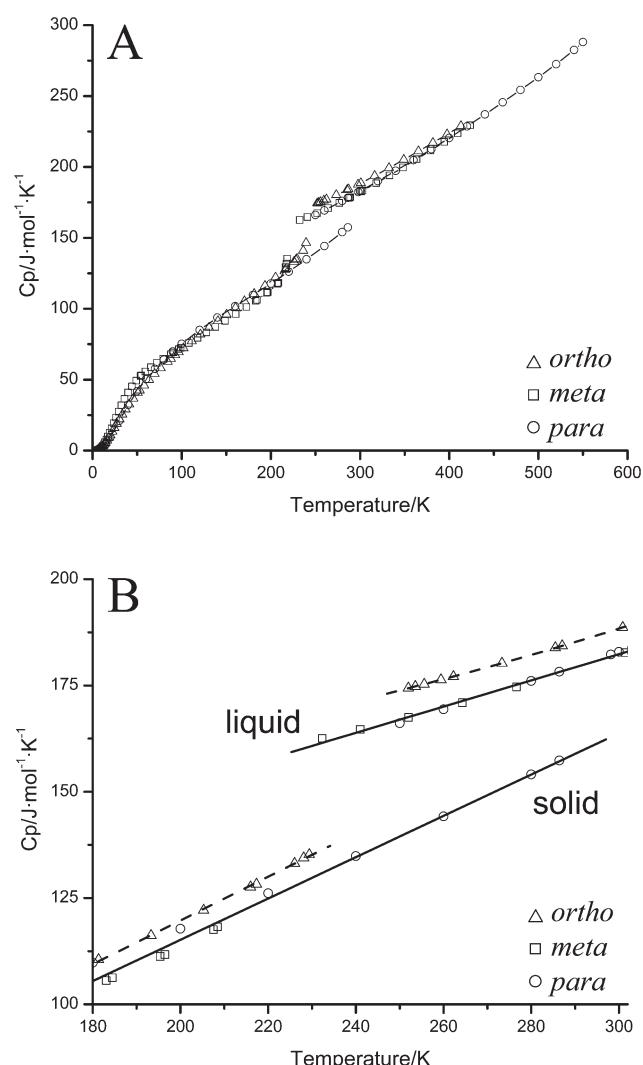
Symmetry effects on the entropy of melting include the residual entropy term of eqn. (3), as discussed by Yalkowsky and coworkers.<sup>7,8</sup> This residual entropy, being a direct contribution of the molecular structure, persists all the way to absolute zero. The third law of thermodynamics states that at absolute zero, all perfect crystalline materials must have the same entropy (assigned a value of zero after Planck), and an empirical observation is that compounds with

symmetrical structures behave as third law violators.<sup>13</sup> From the above considerations, one is compelled to view molecular symmetry, or its effect, as a most primordial type of crystal imperfection.

The treatment presented in the preceding section relies on third law quantities to show in which fashion molecular symmetry affects the entropy and enthalpy of melting. The residual entropy originating from molecular symmetry directly decreases the entropy of melting for symmetrical compounds. However, the condition of equilibrium melting imposes additional heat capacity terms on the expressions for the enthalpy and entropy of melting (eqns. (14) and (15)). The heat capacity integrals in these two expressions, although indirect, are each quantitative effects of molecular symmetry too. If molecular symmetry has the effect of shifting the melting temperature to a different value, the differences in enthalpy and entropy between the solid and liquid phases cannot be independent of where the new melting temperature value happens to be. However, it is the difference in free energy between solid and liquid phases that must be zero when melting occurs. The shift in the (equilibrium) melting temperature, must change the other two quantities of melting, such that the free energy change upon melting does not. In a strict sense, the  $\Delta C_p$  integrals on eqns. (14) and (15) become zero in the trivial case where  $T_1 = T_2$ , given that the  $\Delta C_p$  term itself, as small as it may be, is not zero up to the melting temperature. In practice, one can consider that eqns. (22a) and (22b) are applicable approximations when the difference in melting temperature for the two isomers is rather small. Put another way, the additional effect of symmetry quantified by the heat capacity integrals on both the enthalpy (eqn. (14)) and entropy (eqn. (15)) of melting, is no more than a direct result of the fact that the (equilibrium) melting events of the two isomers do not occur at the same temperature. Eqns. (22a) and (22b) correspond to the hypothetical quantities of melting for species **2** at  $T_1$ , i.e.,  $\Delta H_{m2}(T_1)$  and  $\Delta S_{m2}(T_1)$ , respectively.

The system under consideration here is an idealised one, namely, a system in which going from molecular species **2** to species **1** involves no change other than molecular symmetry and its natural consequences. Wei<sup>5</sup> likened this type of system to one in which a homomorphic molecule can be desymmetrised, as would be the case in an isotopic substitution. The expressions obtained in the present treatment rest on the assumption that molecular symmetry does not change heat capacity for the solid nor the liquid (eqns. (2b) and (2c)), as well as on similar zero point energy for the two isomers. Different symmetry in isomers results in different moments of inertia. Consequently, the assumption  $C_{p1}^L \approx C_{p2}^L$  can only be an approximation, since the contributions of molecular rotations to heat capacity in the liquid are themselves affected by molecular symmetry. However, available data on the heat capacities (solid and liquid) for isomeric systems such as anthracene-phenanthrene<sup>10</sup> and xylene<sup>14–16</sup> isomers suggest that eqns. (2b) and (2c) represent reasonable assumptions. The assumption of equal zero point energy for ideal isomers is a more restrictive one. The packing of molecules in a crystal is mostly driven by the molecular geometry, and molecules tend to form close packing arrangements in organic crystals.<sup>11</sup> In the case of disubstituted benzenes for example, the crystal of the more symmetrical (higher melting) *para*-isomer, usually exhibits more efficient molecular packing than the less symmetrical *ortho*- and *meta*-isomers.<sup>1,9</sup> However, *ortho*- and *meta*-isomers, which have the same symmetry but different shape, often have different melting temperatures. Such differences can be attributed, at least in part, to different lattice energies in their corresponding crystals. The relatively small decrease in lattice energy ( $2\text{--}3\text{ kJ mol}^{-1}$ ) on going from the 1,4-isomer to the 1,2- and 1,3-isomers can lead to an appreciable difference in decrease in melting temperature.<sup>9</sup> It should also be mentioned that in the analysis presented here, it is also implicitly assumed that the zero point vibrational entropy is the same for ideal isomers. Differences in vibrational entropy ( $S_{\text{vib}}$ ) between isomers will have an effect of magnitude equal to  $-TS_{\text{vib}}$  on the free energy of the corresponding solid phase. The isomer with the stronger crystal packing could also have the lower vibrational entropy, this would result in counteracting effects toward the ranking in free energy between the two isomers.<sup>9</sup>

It would be useful to see to what extent a system of real isomers resembles an ideal one. Fig. 2 shows heat capacity data<sup>14–16</sup> for the three structural isomers of xylene: *ortho*, *meta* and *para*. Fig. 2A shows that the heat capacities of the three xylene isomers are similar although not exactly the same in terms of their observed profiles. The heat capacity of both the *ortho*- and *meta*-isomers show signs of premelting, whereas the *para*-isomer does not. The *ortho*-isomer in particular exhibits more significant differences with respect to the other two isomers in both the solid and liquid phases. Fig. 2B shows part of the same data in a narrowed temperature range, such that heat capacity values of solid and liquid can be approximated by straight lines (excluding premelting) around the melting region. The figure shows that the heat capacities for the *meta*- and *para*-isomers are somewhat closer to each other, close enough to allow the use of one common line that correlates with both. In contrast, the *ortho*-isomer shows heat capacity values that are shifted from the common line of the *meta*- and *para*-isomers. The difference in heat capacity for the *ortho*-isomer relative to the other two is even more significant for the liquid than for the solid, as seen in the figure.



**Fig. 2** Heat capacity of xylenes. (A) Heat capacity data of all three isomers of xylene in the solid and liquid states, as a function of temperature. (B) Heat capacity data for the three isomers of xylene in the temperature range surrounding the melting region. The solid lines correspond to the common linear fits for the combined data from the *meta* and *para* isomers in that region (premelting excluded). Dashed lines are the fit of the data for the *ortho* isomer. Data from Chirico *et al.* (Refs. 14–16).

Fitting the lines for the temperature range shown in Fig. 2B, such that one line describes a common heat capacity curve for the solids of the *meta*- and *para*-isomers (as in eqn. (2b)), and another line describes a common heat capacity curve for the liquids of the same isomers (as in eqn. (2c)), would make it possible to explore the applicability of the equations relating the quantities of melting.

Using this approach, the estimated value for the entropy of melting of *p*-xylene (eqn. (15)) is 56.3 J mol<sup>-1</sup> K<sup>-1</sup>, comparable to the experimentally observed value of 59.7 J mol<sup>-1</sup> K<sup>-1</sup>. In this example, eqn. (15) correctly predicts a higher value for the entropy of melting of the more symmetrical isomer, in accordance with the experimental observation. In the case of the enthalpy of melting, the estimate from eqn. (14) is in the order of 14 kJ mol<sup>-1</sup>. Compared to the experimentally obtained value of 17 kJ mol<sup>-1</sup>, the prediction for the enthalpy of melting, although an underestimate, is also in agreement with the experimental observation of higher value for the more symmetric isomer.

It should be pointed out that the analysis presented here does not account for the effects that solid–solid phase transitions have on the observed quantities of melting. The data in Fig. 2 show that the xylenes do not undergo solid–solid phase transitions. This situation, however, is not always the case. Consider for example the structural isomers anthracene and phenanthrene, also listed on Table 1. Using the linear functions published by Allen *et al.*<sup>17</sup> for the heat capacity of the solid (from anthracene) and the liquid (from phenanthrene) it is possible to estimate the quantities of melting for these two isomers as done above for the xylenes. In this case, however, eqn. (15) predicts the entropy of melting of anthracene to be 44 J mol<sup>-1</sup> K<sup>-1</sup>, which happens to be the same as the experimental entropy of melting of phenanthrene, and an underestimate for the actual value for anthracene of 60 J mol<sup>-1</sup> K<sup>-1</sup>. The reason for these results is that phenanthrene undergoes a solid–solid phase transition at 71 °C.<sup>21</sup> Therefore, eqns. (14) and (15) would need to be modified accordingly, in order to account for the effect of a solid–solid transition on the enthalpy and entropy of melting. It is interesting to note that for this system of isomers, eqn. (18) predicts the solubility of phenanthrene to be about 15 times greater than that of anthracene. This is a reasonable estimate, based on the data of Mishra and Yalkowsky,<sup>22</sup> supporting the idea discussed above, that solubility estimations lend themselves to certain simplifications.

Solubility is of special relevance in analyses like the present one. It is a readily measured equilibrium value that quantifies the difference in free energy between a (crystalline) solid phase and its corresponding liquid at a given temperature. Solubility values incorporate the effects of molecular symmetry on the quantities (enthalpy, entropy and temperature) of melting of structural isomers, including the important restrictions from equilibrium melting, as discussed above. In the case of true ideal isomers, namely, if all assumptions of the preceding analysis were exactly applicable, then, by carrying on with the same analysis we obtain:

$$\ln \frac{X_1}{X_2} = \frac{(2T_2 - T)}{T} \ln \frac{\sigma_2}{\sigma_1} \quad (23)$$

The expression above simply restates that, at a given temperature *T*, the difference in free energy (logarithm of solubility ratio) between ideal isomers of different symmetry is exclusively the result of their different residual entropy due to their respective symmetry. As discussed above, the condition of equilibrium melting relates the quantities of melting of the two isomers, so that the subtraction of two non-independent solubility expressions, leaves one of the two melting temperatures as the only degree of freedom. Eqn. (23) is the limiting case for the relationship between the solubilities of ideal isomers. For each assumption of the preceding analysis that is not exactly applicable, there will be a corresponding deviation from eqn. (23). Each of those deviations alters the difference in free energy between isomers from its ideal value of  $-TS$ , making in turn a contribution toward the heat capacity integrals present in eqn. (18) but absent in eqn. (23). Comparison between experimentally obtained solubility ratios and those obtained from eqn. (23), is a quantitative measure of how close a system of structural isomers resembles an ideal system, as defined by the assumptions discussed above.

### Same symmetry, different melting, *ortho*- and *meta*-isomers

The melting parameters for the three xylene isomers are listed on Table 1. For all three parameters of melting, *i.e.*, temperature,

enthalpy and entropy, the order is *para* > *ortho* > *meta*, which is a rather common occurrence.<sup>1,9</sup> Even though the *ortho*- and *meta*-isomers have the same molecular symmetry, higher melting for *ortho*-disubstituted benzenes is not uncommon, and such a situation indicates that there must be yet another factor of common occurrence, not covered by the preceding analysis, relating the melting parameters of *meta*- and *ortho*-isomers. One remaining question is whether such a factor is still related to symmetry or not.

Gavezzotti<sup>1</sup> has interpreted the usually higher melting temperature of *ortho*-disubstituted benzenes over their *meta*-counterparts as confirmation of a compact naphthalene-like pattern adoptable by *ortho*-isomers in the solid phase. This corresponds to differences in crystal packing energy between isomers, as discussed above.<sup>9</sup> It is possible that a different molecular arrangement adopted by each isomer in the solid phase results in different zero point energy for each one (see text below eqn. (10)). If the assumption of equal zero point energy for different isomers is removed from the preceding analysis, a procedure similar to that leading to eqn. (14) gives:

$$\Delta H_{m2} = \Delta H_{ml} - \Delta H^0 + \int_{T_1}^{T_2} \Delta C_p dT \quad (14')$$

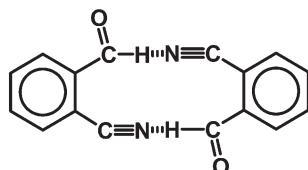
where  $\Delta H^0 = H_2^0 - H_1^0$ , with  $H_1^0$  and  $H_2^0$  denoting the zero point energy of isomers **1** and **2**, respectively. The term  $\Delta H^0$  above is the difference in zero point energy between the two isomers, which accounts for the stronger molecular packing in the higher melting crystal. The terms  $H_1^0$  and  $H_2^0$  are both negative quantities that can be obtained from quantum chemical calculations.<sup>12</sup> Eqn. (14') accounts for an additional enthalpic contribution resulting from the higher crystal packing energy of species **2** (*i.e.*,  $\Delta H^0 = H_2^0 - H_1^0 < 0$ ). In an analogous manner, if by virtue of different molecular arrangements in their corresponding solid phases, the *ortho*- and *meta*-isomers have different zero point energy, it would be possible to apply eqn. (14'). In such a case, the subscripts 1 and 2 in eqn. (14') would be replaced by subscripts *meta* and *ortho*, respectively (*i.e.*,  $\Delta H^0 = H_{ortho}^0 - H_{meta}^0 < 0$ ), and the condition of equilibrium melting would, in turn, dictate that  $T_{ortho} > T_{meta}$ . The considerations leading to, and implications of, eqn. (14'), provide a feasible explanation, in terms of lattice energy, as to why isomers of equal symmetry could exhibit different melting temperatures.

One important and interesting question is whether there is a direct entropic effect for the difference in melting temperature between *ortho*- and *meta*-isomers. Eqn. (14') does not explicitly account for the fact that in addition to higher enthalpy and temperature of melting, *ortho*-isomers often, but very importantly, not always, exhibit also higher entropy of melting than their *meta*-counterparts. Since  $\sigma$  is the same for both *ortho*- and *meta*-isomers, if symmetry is still to play a role in the difference between their melting parameters, such an effect would need to be of a supramolecular nature. This sort of proposition is based on Gavezzotti's<sup>1</sup> observations regarding *ortho*- and *meta*-disubstituted benzenes, observations that can be interpreted as pointing in precisely that direction. Gavezzotti<sup>1</sup> has noted that the *ortho* arrangement can lead to the formation of stable intermolecular dimers in the solid phase, and that such arrangements present the effects of some sort of pseudosymmetry with regard to their usually higher melting temperature. Fig. 3 shows an example of the type of assemblies proposed by Gavezzotti.<sup>1</sup> The molecules in the figure have  $\sigma = 1$ . Consider that the two-molecule assembly is sufficiently stable as to allow for it to be rigidly rotated as one unit (as a quasi-molecule). In such a situation, the supramolecular assembly in Fig. 3 would have a rotational symmetry number of 2. If this type of supramolecular symmetry (or pseudosymmetry) is present, its contribution to the entropy of the solid will be given by an expression of form:

$$S_R = \frac{R}{n} \ln(\Sigma_2^*) \quad (24)$$

where  $S_R$  is the residual configurational entropy contribution resulting from the symmetry of the supramolecular assembly, *n* is the number of molecules forming the assembly, and  $\Sigma_2^*$  denotes

its rotational symmetry number. It is pertinent to clarify that the contribution of supramolecular symmetry to entropy does not make it a requirement for a molecular assembly to actually rotate as a rigid quasi-molecule.

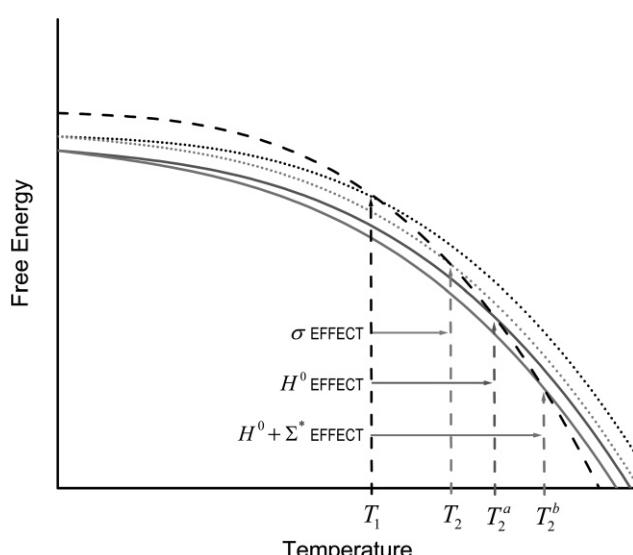


**Fig. 3** Example of the type of molecule pair units possible for *ortho*-disubstituted benzenes, as proposed by Gavezzotti (Ref. 1). Each of the two molecules has  $\sigma = 1$ , whereas the assembly has  $\Sigma^* = 2$ .

Entropy is a state function, and all that is needed is for those molecular configurations obtainable with the hypothetical rigid rotation of the supramolecular assembly, to be part of the total number of possible molecular configurations. The quasi-molecule referred to above is a useful visualisation method, not a mechanistic element. Such a visualisation method should also be a useful tool in simplifying calculations when accounting for undistinguishable molecular arrangements. Eqn. (24) can be viewed as the supramolecular counterpart to eqn. (3), and by a procedure similar to that leading to eqn. (15), its contribution to the entropy of melting can be shown to give:

$$\Delta S_{m2} = \Delta S_{m1} - R \left[ \ln \frac{\sigma_2}{\sigma_1} + \frac{1}{n} \ln(\Sigma_2^*) \right] + \int_{T_1}^{T_2} \frac{\Delta C_p}{T} dT \quad (15')$$

Again, as was the case with eqn. (15), the symmetry term  $\Sigma_2^*$  has a direct contribution to the entropy of melting plus the indirect heat capacity effect. If the subscripts 1 and 2 in eqn. (15') are replaced with *meta* and *ortho*, respectively, the first term inside the brackets vanishes, leaving the direct entropy effect due to the supramolecular symmetry term. Fig. 4 illustrates the effect of different packing energy on the melting temperature for two isomers with equal molecular symmetry (eqn. (14')). The figure also illustrates the effect that different supramolecular symmetry (eqn. (15')) could have on the melting temperature of two isomers of equal molecular symmetry.



**Fig. 4** Effect of zero point energy and supramolecular symmetry on melting. The dashed and dotted lines, along with  $T_1$  and  $T_2$ , are the same as in Fig. 1. The point  $T_2^a$  corresponds to the additional change in  $T_2$  resulting from different zero point energy between the two isomers (eqns. (14') and (15')). Point  $T_2^b$  corresponds to the additional change in  $T_2$  resulting from the different zero point energy well as from the supramolecular symmetry of the higher melting one (eqns. (14') and (15')).

## Concluding remarks

Symmetry is a molecular attribute whose effects find their way manifested at the bulk property level, up to a certain point. The melting point, that is. Symmetry effects are part of the bulk properties of the solid up to, and including its transition into the liquid phase, *i.e.*, the point at which such effects become energetically spent. The analysis presented here, although a simplified one, provides a conceptual connection among the quantities of melting as they are affected by molecular symmetry. It helps explain why a symmetric molecule, which has higher entropy (closer to that of the liquid), could also, as is often the case, undergo a greater entropy gain upon melting, than a non- (less) symmetrical one. The analysis also shows that due to the condition of equilibrium melting, molecular symmetry has additional, non-direct effects on both the enthalpy and entropy of melting. Entropy of melting is a determining factor on the ideal solubility of organic compounds, it follows that molecular symmetry should have an explicit effect on solubility.

The existence of structural isomers with equal molecular symmetry but different melting properties is evidence that molecular symmetry alone does not account for all the differences in melting parameters between structural isomers. Differences in packing energy between isomers of equal symmetry can explain the higher melting of one over the other. However, the fact that the difference in melting parameters between *ortho*- and *meta*-disubstituted benzenes is less a function of their chemical nature than of the arrangement of their molecules in space,<sup>1</sup> leaves room for the possibility of another geometrical factor, not previously considered, at play. These considerations lead to proposing the possibility of a supramolecular symmetry effect like that of eqn. (24). It should be noted that the idea of supramolecular symmetry is not unprecedented, since it is analogous to the concept of non-crystallographic symmetry (a localised, rotational symmetry involving assemblies of molecules) originally introduced by Rossmann<sup>23</sup> for biomolecules. More recently,<sup>24</sup> high symmetry crystal supramolecularity has been reported. Nevertheless, the effect of supramolecular symmetry on melting awaits experimental confirmation or disproving, and with basis on the estimations presented above, one can say that structural isomers may not provide the most suitable system for testing the hypothesis embodied in eqn. (24). For this purpose, study of the melting of certain types of polymorphic systems may prove to be more suitable systems. In these cases, eqn. (2c) will be an exact property of the system instead of an assumption, and the applicability of eqn. (2b) can be assessed, and corrected if necessary, up front. The type of analysis used here for the melting of structural isomers can be also useful in studying the melting of racemic mixtures, where the apparent entropy of mixing of optical isomers in the liquid state is sometimes non ideal, even negative.<sup>25</sup> In any case, however, it is unlikely that considerations based on equilibrium thermodynamics alone will be able to accomplish the task. Instead, a combination of molecular modelling and thermal measurements will be necessary.

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