Research article

Thermodynamic explanation and criterion for the exhibition of melting inability in molecular species

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Abstract: Thermodynamic properties of matter e.g., melting point, are important for various applications. However, in some substances the primary observed effect upon heating is decomposition which in some cases is accompanied by fluidization. Thus, it would be very useful to be able to predict if a given substance will be able to melt or will exhibit melting inability upon heating. In this work, a thermodynamic explanation for the melting inability of molecular solids is provided and a corresponding criterion is proposed for the prediction of melting ability or inability of a given substance. One key concept is to study the strength of the weakest chemical bond rather than overall enthalpy of reaction. This arises from the fact that if decomposition occurs, then, regardless of the extent of decomposition, the transition cannot be considered to be melting. The criterion can be combined with sophisticated modeling in order to derive accurate values. Here, a simple method is proposed and an approximate index is developed which allows for a rapid and massive implementation of the criterion. The index is based on the concept of group contributions methods (estimation of the enthalpy of the maximum possible interactions, ΔH_{max}) and on a distorted version of Trouton's rule (correlation of ΔH_{max} with the heat required for melting). The correlation factor ($x_{melting}$) was found to be equal to 40.6%. The index is successfully applied in various organic substances, including (bio)molecules of pharmaceutical/nutraceutical interest. Index values between −30 and 0 correspond to marginal cases of rather high uncertainty. Positive index values clearly point out melting inability. The proposed index successfully predicts the melting ability/inability in more than 80% of the studied substances.

Keywords: melting; inability; decomposition; entropy; enthalpy; simultaneous

1. Introduction

Thermal properties of matter are of great importance since they are involved and needed in order to understand/design numerous phenomena and processes. The thermal thermodynamic properties, such as melting point, heat of fusion and specific heat capacity, are perhaps among the most common thermal properties. The knowledge of such parameters allows for an optimum design of a process. Similarly, the thermal stability of a substance is also quite important and must be taken into account in various cases e.g., during material processing, food sterilization and drug preparation. Thermal thermodynamic properties are measured in calorimeters e.g., Differential Scanning Calorimeter (DSC). The interpretation of data from such instruments is not always an easy procedure. Recently, in previous works of the author, it was reported that some organic molecules, namely silybin [1], gallic acid [2] and quercetin [3], are unable to actually melt (that is to melt without decomposing) and their softening point was termed as (solid-liquid) thermochemical transition. In other words, in some molecules, melting and decomposition (thermal stability) are "mixed up". Consequently, a tool for predicting such behavior may be useful for research and industry e.g., either to be suspected when interpreting a DSC curve or in the absence of available data and instruments in order to predict that a substance is likely to decompose and thus to avoid high temperature processing e.g., to avoid encapsulating a drug in a polymer matrix through melt extrusion.

In the literature, though there are no references regarding thermochemical transition, it has been reported that various organic substances do not exhibit melting prior to decomposition e.g., for quercetin dihydrate [4], rutin dihydrate [4] and dehydrated lithium potassium tartrate [5]. For succinic acid, it has been reported [6] that the variation in the reported values of its melting point most likely arises from the fact that decomposition and/or dehydration of the acid group occurs during melting. In the Handbook of Chemistry and Physics [7], in the section with the phase transitions data, for numerous substances instead of melting point, the word "dec" (from decomposition) is mentioned. Interestingly, for various substances, the same can be observed for the boiling point. Such substances with melting/boiling inability are mostly organic and inorganic substances with co-existence of covalent and ionic bonds, e.g., organic salts [7]. Also, a special type of organic salts, namely, ionic liquids are unable to boil at atmospheric pressure, but also some decomposition is observed even under vacuum distillation [8]. In the Handbook [7], besides the word "dec", no other data are given e.g., the state of matter of decomposition products. Of course, there is no reason to assume that liquid is formed in all these cases. Aragonite (a crystalline form of calcium carbonate) is known to decompose [7] into solid CaO and gaseous CO_2. Thus, not in all these cases of organic and inorganic salts can be claimed that a solid-liquid thermochemical transition occurs. The solid-liquid thermochemical transition can be considered as a special case of melting inability in which the residue or some other decomposition product is liquid. However, independently of the state of matter of the decomposition products, fundamentally, these substances exhibit the very same property e.g., quercetin and aragonite exhibit the very same property of melting inability.

The completely different structure of such substances renders it difficult to find a structure-property relationship for substances exhibiting melting inability. The finding of a such relationship could be facilitated by studying substances of a similar nature e.g., substances only with covalent bonds,

organic substances with co-existence of covalent and ionic bonds, inorganic substances with co-existence of covalent and ionic bonds etc. For molecular species (composed solely of covalent bonds), some elementary structure-property relationship has been reported in previous studies of the author, based on the fact that the vast majority of such molecules exhibit a strong capability for formation of hydrogen bonding. More specifically, it is known that groups e.g., OH groups, which are involved in strong molecular interaction i.e., hydrogen bonding, absorb infrared radiation of lower frequency compared to one of the free groups [9]. This shifting is related to the alteration of the force constant which is translated to lower chemical bond strength for a hydrogen bonded group than for a free group. In other words, the strong molecular interaction weakens the chemical bond. Indeed, in various cases, reported by the author, by studying with Fourier Transform Infrared Spectroscopy substances heated just above their softening point, it was confirmed that the majority of the decomposed groups were the strongly bonded ones. Thus, it was reported [1,3] that hydrogen bonding has a dual effect on the melting inability: (1) Constrains melting due to the strong attraction forces between molecules and (2) facilitates decomposition through the weakening of chemical bonds.

This elemental structure-property relationship seems to be in the right direction, however, it cannot be the full or exclusive explanation for the exhibition of melting inability in molecular species. For example, alcohols, amines etc. also exhibit a strong hydrogen bonding capability. Similarly, carboxylic acids are known to form dimers through hydrogen bonding even in the vapor phase [10]. In such substances, does not hydrogen bonding result in the weakening of chemical bonds and the corresponding facilitation of decomposition? In such substances, is melting not constrained by the extensive hydrogen bonds? Such questions, ultimately, can be reduced to the following question: Why are some molecules able to melt and some others exhibit melting inability? The scope of this work is to provide insights regarding this latter question.

2. Theoretical analysis

2.1. General considerations

The basic concept behind the index is a criterion based on the comparison of the change of Gibbs free energy ΔG during melting and decomposition. In general, ΔG is influenced by two contributions, namely, one from the enthalpy change ΔH and one from the entropy change ΔS, and is equal to:

$$\Delta G = \Delta H - T \Delta S \tag{1}$$

At the melting point, the ΔG of melting is equal to zero while for temperature higher and lower than the melting point, the ΔG of melting is respectively negative and positive and thus melting is respectively spontaneous (thermodynamically favored) and non-spontaneous. However, if at a given temperature, ΔG of decomposition is equal or even lower than the corresponding value for melting, then decomposition will be favored over melting. Thus, the criterion C for the ability or inability of exhibition of melting is the following:

$$C = \Delta G_{melting} - \Delta G_{decomposition}$$

$$if\ C < 0 \Rightarrow \Delta G_{melting} < \Delta G_{decomposition} \Rightarrow melting \tag{2}$$

$$if\ C \geq 0 \Rightarrow \Delta G_{decomposition} \leq \Delta G_{melting} \Rightarrow inability\ for\ melting$$

where:

$\Delta G_{melting}$, the specific Gibbs free energy change upon melting at a given temperature.

$\Delta G_{decomposition}$, the specific Gibbs free energy change upon decomposition at a given temperature.

From Eqs 1 and 2 it follows that:

$$C = \Delta H_{melting} - T \times \Delta S_{melting} - \Delta H_{decomposition} + T \times \Delta S_{decomposition} \Rightarrow$$

$$C = (\Delta H_{melting} - \Delta H_{decomposition}) - T \times (\Delta S_{melting} - \Delta S_{decomposition}) \tag{3}$$

where:

$\Delta H_{melting}$, the specific enthalpy change upon melting at a given temperature.

$\Delta S_{melting}$, the specific entropy change upon melting at a given temperature.

$\Delta H_{decomposition}$, the specific enthalpy change upon decomposition at a given temperature.

$\Delta S_{decomposition}$, the specific entropy change upon decomposition at a given temperature.

In the case of melting, the increase of entropy arises from the collapse of the crystalline (ordered) structure and the breaking of a portion of intermolecular forces. However, decomposition also leads to collapse of the crystalline structure and breaking of intermolecular forces (and thus results in a corresponding increase in entropy). In addition, it results in an increased number of species and phases which can be translated to higher entropy values. Molecules in the solid state have practically only vibrational motion while in the liquid and vapor state, molecules, additionally have rotational and translational motion. In the liquid state, there are more intermolecular interactions than in the vapor state, thus some motions e.g., rotational are likely to be constrained. Consequently, the number of available states (and thus entropy) are higher for gases than liquids and correspondingly the same holds for liquids over solids. Of course the number of states of a system depends also on the number of molecules. In the case of breaking of only one chemical bond per molecule, at least two new molecules will be formed for non-cyclic molecules. Typically, at least one of the decomposition products is a gas. Thus, for both reasons (increase in number of molecules and production of phase with increased molecular motion) the breaking of one mole of chemical bonds will most likely result in higher entropy than the increase in entropy during the transition of one mole from the solid to the liquid state.

Thus, though exceptions may exist, it seems reasonable to assume that as a general rule, the increase in entropy during decomposition is higher than the increase in entropy during melting. Since decomposition is entropically favored over melting, its contribution to ΔG is more negative than the one of melting. Consequently, the second term in the right hand side of Eq 3, that is, the term $-T \times (\Delta S_{melting} - \Delta S_{decomposition})$, can be considered to be positive and thus, from an entropy point of view, the value of criterion C tends to become greater than zero (decomposition tends to be thermodynamically favored over melting due to entropic reasons). Thus, it seems sufficient to compare the ΔH values, that is, the criterion C expressed by Eq 2 can be reduced to an approximate criterion AC which takes into account only the enthalpy values:

$$AC = \Delta H_{melting} - \Delta H_{decomposition}$$

$$if\ AC < 0 \Rightarrow \Delta H_{melting} < \Delta H_{decomposition} \Rightarrow melting \tag{4}$$

$$if\ AC \geq 0 \Rightarrow \Delta H_{decomposition} \leq \Delta H_{melting} \Rightarrow inability\ for\ melting$$

It is worth to mention that in order to be feasible to calculate the values of $\Delta H_{decomposition}$ and $\Delta S_{decomposition}$, it is required the knowledge of the exact decomposition reaction(s). For any given

substance this is a very difficult task. Thus, Eqs 3 and 4 are not easily and massively implementable for any given substance.

2.2. Approximate melting inability index, AMI

Before proceeding, the following key aspect must be taken into account: The extent of decomposition is important from a practical/technological point of view. For example, we may consider a polymer which is unable to melt and instead, it exhibits a solid-liquid thermochemical transition. If the extent of decomposition during the thermochemical transition is very low e.g., 0.05%, then it follows that, practically, the polymer can be thermally processed without any severe deterioration of its properties. However, from fundamental/scientific point of view, the occurrence of decomposition itself is crucial and not its extent, since even in the case in which only one chemical bond per molecule breaks during softening (that is, one mole of chemical bonds per mole of molecules), then, any macroscopically observed fluidization (transition) cannot be considered to be melting. Thus, as for the state of matter of the decomposition products discussed in the Introduction section, the extent of decomposition, fundamentally, is also a secondary issue. However, the enthalpy of reaction (decomposition), which appears in Eq 4, is equal to the difference of the sum of the enthalpies of formation of the products and the enthalpy of formation of the reactant. In other words, the enthalpy of decomposition in Eq 4 is influenced by the extent of decomposition and the nature of the decomposition products. In order to take into account the above mentioned aspect (that the extent of decomposition is not important in order to claim that a substance exhibits melting inability), instead of using the enthalpy of reaction, the enthalpy (dissociation energy) of the weakest chemical bond will be taken into account. For this purpose the approximate melting inability index is proposed and is expressed as follows:

$$AMI = Q_{melting} - Q_{decomposition}$$

$$If\ AMI < 0\ \Rightarrow the\ substance\ will\ melt \tag{5}$$

$$If\ AMI \geq 0\ \Rightarrow the\ substance\ is\ unable\ to\ melt$$

where:
AMI, approximate melting inability index.
$Q_{melting}$, the heat required for melting one mole of substance.
$Q_{decomposition}$, the heat required for breaking one mole of (the weakest) chemical bonds of the substance.

In order to estimate the value of the criterion/index, values for $Q_{melting}$ and $Q_{decomposition}$ are needed. Such expressions can be derived by sophisticated models based on statistical thermodynamics, molecular dynamics, quantum mechanics etc. Values derived from such methods are expected to be of high accuracy. However, these methods are time consuming, require appropriate software etc. Here, a much simpler route will be proposed.

$Q_{melting}$ is directly related to the specific enthalpy of fusion and can be derived from available group contribution methods. As mentioned above, more accurate expressions for $Q_{melting}$ and $Q_{decomposition}$ could be derived by statistical thermodynamics based-models or quantum mechanics-based models. For sake of simplicity, here, the order of magnitude (and not accurate values) of these terms will be considered and used for developing an easily and rapidly calculable index. More

specifically, the terms $Q_{melting}$ and $Q_{decomposition}$ will be approximated by taking into account the corresponding values of the enthalpy of physical interactions and chemical bonds. Clearly, the magnitude of heat of melting does not depend exclusively on the values of the enthalpy of intermolecular interactions; however, it is influenced by it. Due to various reasons e.g., stereochemical factors, not all the maximum number of intermolecular interactions can be formed. In addition, in order for melting to occur, not all the physical interactions are needed to break but only a portion of them. Thus, for the approximation of the value of the term $Q_{melting}$ of the index, a percentage (%) of the enthalpy related to the maximum possible number of intermolecular interactions in which one molecule can take part in (ΔH_{max}) will be used, that is:

$$Q_{melting} = \frac{x_{melting}}{100} \times \Delta H_{max} \tag{6}$$

where:

ΔH_{max}, enthalpy related to the maximum possible number of intermolecular interactions in which one molecule can take part.

$x_{melting}$, the percentage of ΔH_{max} which corresponds to heat required for the melting (expresses the percentage of maximum possible formed intermolecular interactions that must be broken in order for melting to occur). A universal (constant) value will be used for $x_{melting}$ while the value of ΔH_{max} for each given substance will be estimated by a simple group contribution method. In what follows the procedure for the estimation of $x_{melting}$ and ΔH_{max} is presented.

To enable the discussion for the estimation of ΔH_{max}, some specific examples will be presented. Ethanol has one C–O–H group and 5 C–H groups that could take part in intermolecular interactions. Each of the 5 C–H groups can take part in one interaction (e.g., van der Waals), while the C–O–H group can take part in up to three hydrogen bonds (one due to H as proton donor and two due to O which can accept two protons). Thus, one mole of ethanol can take part in up to a maximum of 8 physical interactions. Using some average values for the enthalpy of hydrogen bond and van der Waals interaction, respectively equal to 25 kJ/mol and 1 kJ/mol, it follows that for one mole of ethanol, the maximum enthalpy related to intermolecular forces will be equal to $1 \times 3 \times 25 + 5 \times 1$ kJ. Thus, for any given substance the enthalpy related to the maximum possible number of intermolecular interactions can be expressed by an equation of the following form:

$$\Delta H_{max} = \sum (N_{lp} \times \Delta H_{lp} + N_p \times \Delta H_p + N_{ar} \times \Delta H_{ar} + N_{hb} \times s_{hb} \times \Delta H_{hb}) \tag{7}$$

where:

ΔH_{lp}, enthalpy of intermolecular interaction between low polarity groups e.g., in the order 0.1–1 kJ/mol.

ΔH_p, enthalpy of intermolecular interaction between polar groups e.g., in the order 1–10 kJ/mol.

ΔH_{ar}, enthalpy of intermolecular interaction between aromatic rings e.g., in the order 8–12 kJ/mol.

ΔH_{hb}, enthalpy of intermolecular interaction between hydrogen bonded groups e.g., in the order 10–100 kJ/mol.

N_{lp}, number of low polarity groups (e.g., C–H) that interact through weak interaction.

N_p, number of polar groups (e.g., C–O) that interact through polar interactions.

N_{ar}, number of aromatic rings within the molecule.

N_{hb}, number of groups able to form hydrogen bonds.

s_{hb}, sum of number of proton donor and acceptor sites of each group able to form hydrogen bonds e.g. for O–H group $s_{hb} = 3$.

Before proceeding, it should be stressed that groups that can form hydrogen bonds but only either as proton donors or acceptors e.g., the carbonyl group, can be taken into account either in the category of polar groups or in the category of hydrogen bonded groups depending on what other groups exist within the molecule. For example, in the case of acetone, the carbonyl group will be considered a polar group, since in pure acetone the carbonyl group cannot take part in any hydrogen bonding, while in flavonoids where hydrogen bonded groups exist, the carbonyl group will be considered a hydrogen bonded group with two sites. For implementing Eq 7, are needed the structural chemical formula of the substance and the average enthalpy values presented in Table1.

Table 1. Range of magnitude of enthalpy of physical interactions and proposed average value for calculating ΔH_{max} from Eq 7.

Group	Representative range of values of the enthalpy of interaction, kJ/mol	Average proposed enthalpy value, kJ/mol
Non-polar/low polarity groups e.g. C-H	0.1–1	$\Delta H_{lp} = 1$
Polar groups e.g. C-O, C-N	1–10	$\Delta H_p = 10$
Aromatic ring	8–12 [11]	$\Delta H_{ar} = 10$
Hydrogen bond groups e.g. O-H, COOH	10–100	$\Delta H_{hb} = 25$

For the estimation of the value of $x_{melting}$ various (62) organic substances of quite different polarity and molecular weight were considered. The substances were categorized into five groups according to their characteristic group (hydrocarbons, ethers, ketones, acids and alcohols). For each one of these substances, the value of ΔH_{max} was calculated from Eq 7 and the heats of melting were collected from the NIST Chemistry Webbook [12]. These values are presented in Tables S1–S5 of the supporting information. For each one of these substances, the value of $x_{melting,i}$ was calculated from the following equation:

$$\Delta H_{melting,i} = \frac{x_{melting,i}}{100} \times \Delta H_{max,i} \Rightarrow$$

$$x_{melting,i} = 100 \times \frac{\Delta H_{melting,i}}{\Delta H_{max,i}}$$

(8)

where:

$x_{melting,i}$, is the value of parameter $x_{melting}$ (expressed in %) for substance i.

$\Delta H_{melting,i}$, the enthalpy of fusion (in kJ/mol) of substance i. These values were collected from literature [12].

$\Delta H_{max,i}$, the value of $\Delta H_{max,i}$ (in kJ/mol) for substance i. These values were calculated from Eq 7.

Then, the average value and standard deviation of $x_{melting,i}$ were calculated. The average value was set equal to $x_{melting}$. The above mentioned substances were chosen since they can be considered as "simple" compounds with indisputable melting ability. On the contrary, complex molecules e.g.,

gallic acid exhibit melting inability and various literature reported values for heat of fusion have a questionable physical meaning. Thus, for the estimation of $x_{melting}$, only substances with well-established melting ability were considered.

For the value of $Q_{decomposition}$, the values of the specific chemical bond strengths, which can be found in various sources [7,13], can be used. The heat required to break one mole of chemical bond is simply:

$$Q_{decomposition} = \Delta H_{chemical\ bond} \tag{9}$$

where:

$\Delta H_{chemical\ bond}$, the bond strength of the weakest chemical bond within a given molecule, expressed in kJ/mol.

In order to be feasible to calculate and implement the index easily and rapidly, some further simplification will be made. Above (Table 1), the typical range for the enthalpy of various intermolecular forces was given as order of magnitude (e.g. 1–10 kJ/mol). The order of magnitude of the bond strength of covalent chemical bonds is 100–1000 kJ/mol. Thus, for $\Delta H_{chemical\ bond}$, a universal constant value of 100 kJ/mol will be used. As mentioned above, accurate estimation of ΔH_{max} and $\Delta H_{chemical\ bond}$ would require sophisticated modeling. Since, here, a simplified route was followed, the values of ΔH_{max} lack in accuracy. Thus, there is no point to try and find which chemical bond is the weakest in a given molecule by trying to find its average strength from Handbooks. Using the value of 100 kJ/mol for $\Delta H_{chemical\ bond}$, simply, a reference point for the order of magnitude of chemical bond strength is provided. Thus, Eq 9 can be reduced to:

$$Q_{decomposition} = 100 \tag{10}$$

By taking into account Eqs 5–10, it follows that the approximate melting inability index (AMI) is:

$$AMI = \frac{x_{melting}}{100} \times \Delta H_{max} - 100 \Rightarrow$$

$$AMI = \frac{x_{melting}}{100} \times \sum (N_{lp} \times \Delta H_{lp} + N_p \times \Delta H_p + N_{ar} \times \Delta H_{ar} + N_{hb} \times s_{hb} \times \Delta H_{hb}) - 100 \tag{11}$$

The units of AMI are kJ/mol.

As a summary, the concept behind the index is the following: The extent of decomposition is not important. The entropy change during decomposition is expected to be higher than the one of melting. Thus, if the order of magnitude of the enthalpy required for melting is high and approaches the order of magnitude of the strength of chemical (covalent) bonds, then it is likely that decomposition will be thermodynamically favored over melting and consequently the substance will exhibit melting inability instead of melting. The more positive the value of AMI is, the higher is the probability for exhibition of melting inability.

3. Results and discussion

3.1. Value of $x_{melting}$

Before proceeding, it is worth to mention that the concept behind the procedure for the estimation of $x_{melting}$ can be considered as a distorted version of Trouton's rule. As mentioned in the previous section, the ΔH_{max} cannot be directly translated into enthalpy of melting; however, it influences its value. Here, the Trouton's rule [14,15] must be recalled, which states that in various liquids, the value of molar entropy of vaporization is practically the same and fluctuates around 85 J/mol/K. Non polar liquids, such as nitrogen etc., have lower values e.g., 70 J/mol/K while strongly polar liquids like water and ethanol have higher values e.g., 110 J/mol/K. Despite the fact that various such liquids deviate from Trouton's rule, the order of magnitude of entropy of vaporization is the same with other liquids. This universal order of magnitude of the entropy of vaporization is derived by quite different values of molar enthalpy of vaporization which are "normalized" by dividing them by the boiling temperature. Here, the values of molar enthalpy of melting are "normalized" by dividing them with ΔH_{max}. As for heat of melting, the parameter ΔH_{max}, though indirectly, is also affected by the molecular weight and the polarity of the substance. Thus, the ratio of these two parameters (that is, $x_{melting}$), as for the case of entropy of vaporization, for various substances fluctuates within a narrow range and is in the same order of magnitude for quite different substances (polar/non-polar, aliphatic/aromatic etc.).

The above are evident for the case of some n-alkanes in Figure 1. More specifically, in Figure 1a, the ΔH_{max} and $\Delta H_{melting}$ are plotted versus melting point. As can be seen, both the enthalpies exhibit an increasing trend with the melting point. Thus, in the correlation plot of ΔH_{max} and $\Delta H_{melting}$ (Figure 1b) a fairly acceptable linear relationship can be observed, indicating that the ratio of ΔH_{max} and $\Delta H_{melting}$ is rather constant. Similar observations and conclusions can be made for the case of some 1-alcohols, in the respective plots in Figure 2.


(a)   (b)
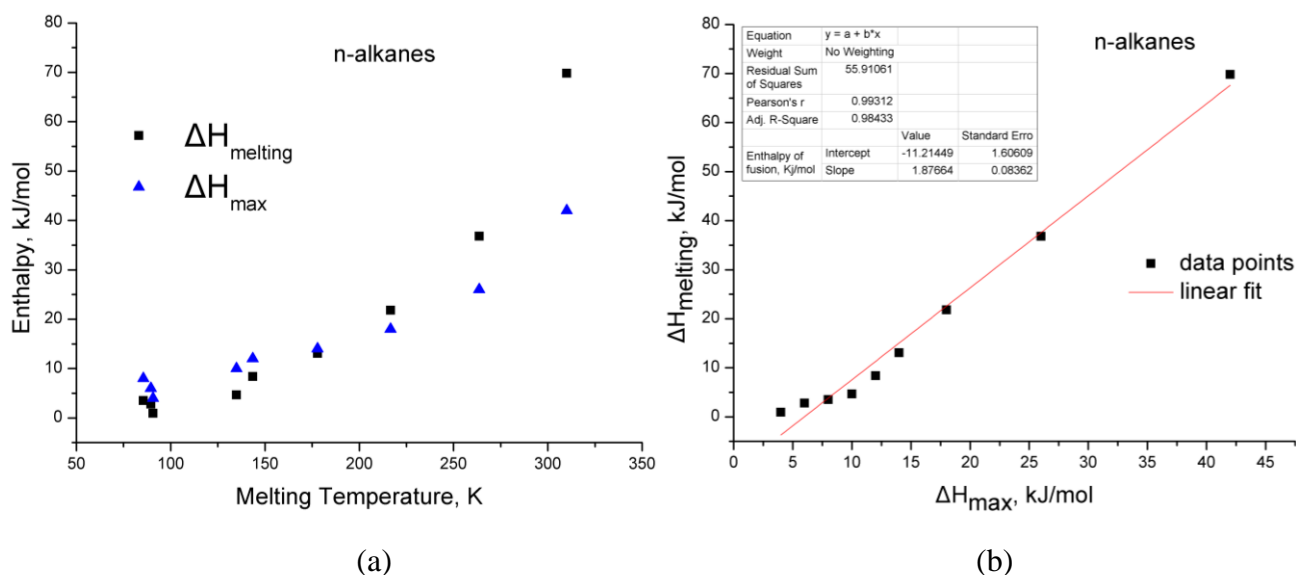
Figure 1. Correlation plots for n-alkanes: (a) $\Delta H_{melting}$ and ΔH_{max} versus melting temperature and (b) $\Delta H_{melting}$ versus ΔH_{max} and their linear correlation.

(a)   (b)
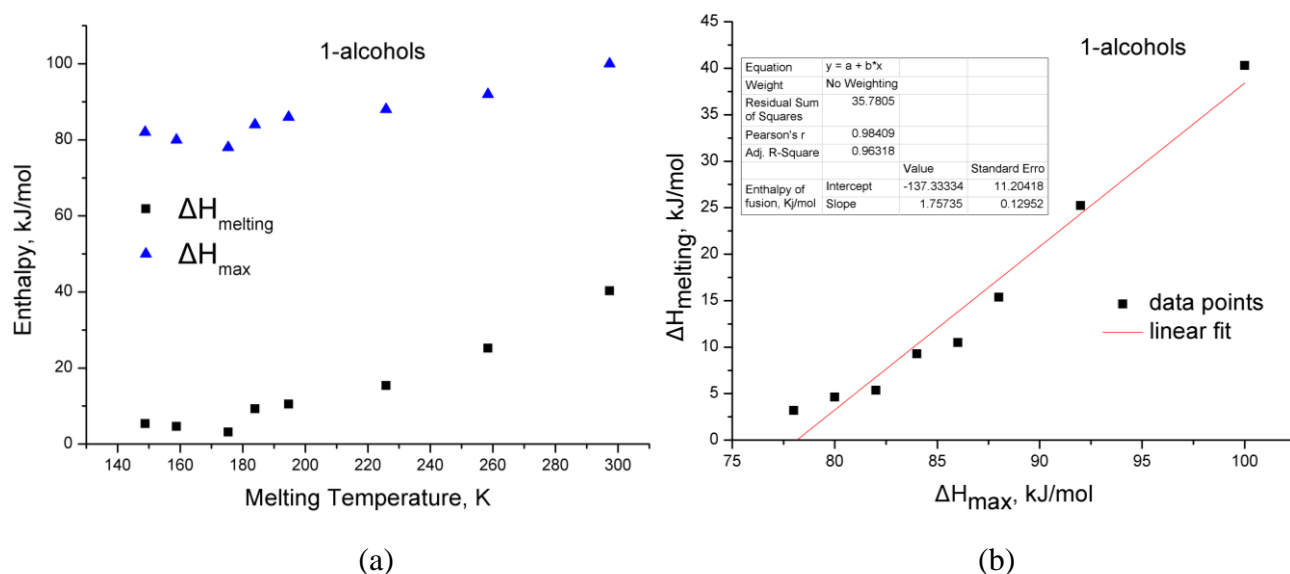
Figure 2. Correlation plots for 1-alcohols: (a) $\Delta H_{melting}$ and ΔH_{max} versus melting temperature and (b) $\Delta H_{melting}$ versus ΔH_{max} and their linear correlation.

Of course, if alkenes or aromatic hydrocarbons, or phenols are included, the linearity is not that high but the positive correlation exists. Thus, the ratio of ΔH_{max} and $\Delta H_{melting}$ (that is $x_{melting}$) is of the same order of magnitude for various hydrocarbons. In Figure 3a, the % frequency plot for $x_{melting}$ of the five considered groups is shown, that is, in the X-axis one can read the value of $x_{melting}$ and in the Y-axis one can read the % number of substances exhibiting this value of $x_{melting}$. As can be seen in Figure 3a, the vast majority of hydrocarbons (linear/cyclic/aromatic, saturated etc.) exhibits a value of $x_{melting}$ in the range 40–70%. Polar substances (acids and alcohols) exhibited the lowest values of $x_{melting}$(10–20%). The vast majority of substances of medium polarity (ethers and ketones) exhibited intermediate values for $x_{melting}$(40–50%). In the cumulative frequency plot for all five groups, which is presented in Figure 3b, it can be seen that 51.6% of all substances exhibit value of $x_{melting}$lower than 30%, while 79% of the substances exhibit values of $x_{melting}$ lower than 50%. In Table 2, the average values and the standard deviation (absolute and %) for each one group and for all substances are presented. The value of $x_{melting}$ was set equal to the average value from all substances (40.6%). This value suggests that around 40% of the maximum possible intermolecular forces of a molecule break upon melting. This value, which was calculated from ΔH_{max} and $\Delta H_{melting}$, is close and of the same order of magnitude to the value of $x_{melting}$ for the vast majority of the examined substances. Thus, it can be considered that by following the opposite procedure and using $x_{melting}$and ΔH_{max}, an acceptable approximation of the order of magnitude of (actual or hypothetical) $Q_{melting}$ can be reached (obviously for substances with melting inability the prediction of the value of $Q_{melting}$ corresponds to a hypothetical non-existing parameter).

(a)   (b)
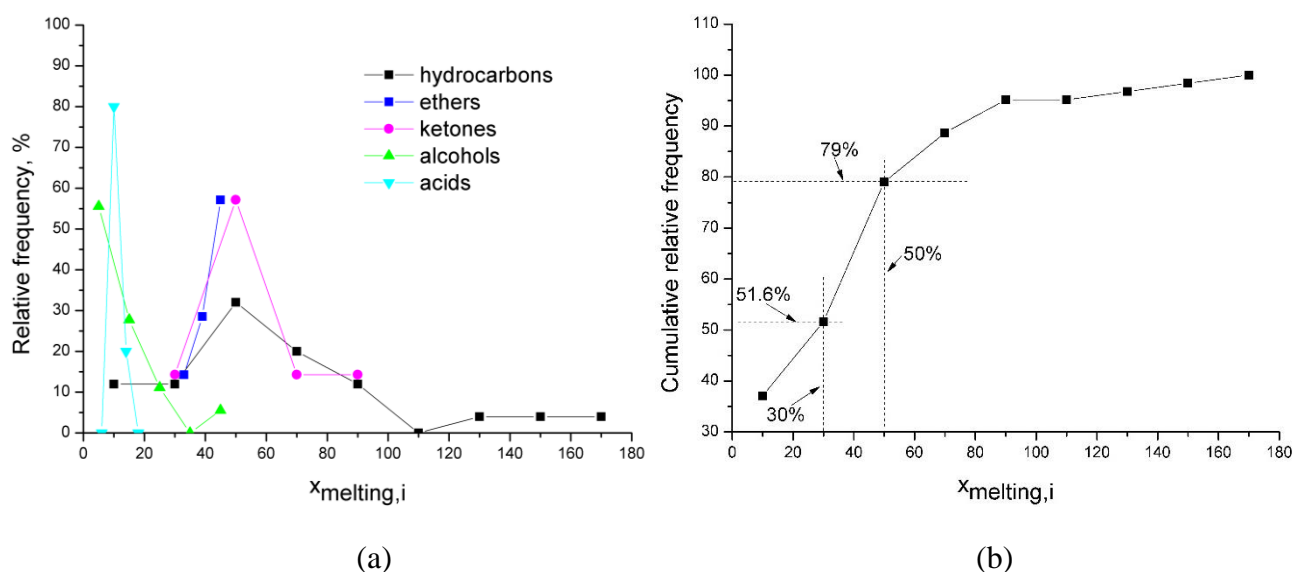
Figure 3. (a) Relative (%) frequency plot for $x_{melting,i}$ for substances of groups of various polarity and (b) Cumulative relative frequency for all substances.

Table 2. Average value and standard deviation (absolute and %) of $x_{melting}$, as calculated from groups of various polarity and for all substances (see Tables S1–S5 in supporting information for more details).

	$x_{melting}$		
	Average value	Standard deviation	% Standard deviation
hydrocarbons	61.9	39.3	63.5
ethers	41.3	6.1	14.8
ketones	57.5	19.1	33.2
acids	9.6	1.7	17.6
alcohols	12.8	9.3	73
all substances	40.6	34.6	85.2

Finally, it is worth mentioning that perhaps it would be more accurate to use different values for $x_{melting}$, depending on the polarity of each substance. However, as mentioned above, the value of the proposed method is its simplicity and thus it was chosen to use a single universal value. In addition, for simple molecules the classification as low, medium or highly polar is straightforward but for complex molecules containing a wide variety of groups, the classification as medium or highly polar may be to some extent subjective.

3.2. Prediction of melting ability/inability in various organic molecules

The *AMI* index was calculated for 100 organic substances. The values of the *AMI* index for the 62 substances, which were mentioned in the previous section and were used for the derivation of the value

of $x_{melting}$ are presented in Table S6 in the supporting information. For all these substances, the AMI index is negative, that is, it correctly predicts the melting ability of these 62 substances. In Table 3, the values of AMI index for other 38 substances are presented. For all these substances, the parameters used for the calculation of ΔH_{max} are presented in Tables S7 and S8 of the supporting information. In the last column of Table 3 for each substance, information is provided that enable the discussion about the confirmation of the index's predictions. This information is based on the NIST Chemistry Webbook [12], which takes into account multiple sources for every substance and the reported data are critically evaluated. Though only a thorough experimental study for each substance would provide an indisputable confirmation of the predictions, the lack of data in NIST Chemistry Webbook for a given substance can be considered as strong evidence for melting/boiling inability, especially if the lack of data concerns common substances with great scientific and industrial interest e.g., amino acids. For example, for glycine, only some sublimation point is given in NIST Chemistry Webbook. However, it is difficult to believe that the lack of melting/boiling data arises from the fact that nobody ever bothered to measure the melting or boiling point of glycine. This lack of data strongly suggests inability to measure the melting point due to the melting inability of glycine (this will be further discussed below).

In previous studies of the author, gallic acid (number 4 in Table 3), quercetin (number 29 in Table 3) and silybin (number 30 in Table 3) were reported to exhibit melting inability. Quercetin and rutin dihydrate have been reported to exhibit melting inability by other authors. The AMI index for rutin (number 31 in Table 3) was calculated without taking into account any hydrated water (if water is taken into account, then the value will be more positive), but its value as for gallic acid, quercetin and silybin is positive and quite higher than zero. Thus, the AMI index correctly predicts the confirmed melting inability in these four substances. It is worth to mention that in NIST Chemistry Webbook, no melting data are reported for gallic acid and rutin (this supports the above claiming for glycine), while melting data are (erroneously) reported for quercetin and silybin. Boiling data are not reported for any of these substances. Interestingly, for succinic acid (number 3 in Table 3) melting data are reported but no boiling data. However, in the literature, it has been reported that the variations in the value of the melting point of succinic acid must be related to dehydration/decomposition [6]. This, in combination with the absence of boiling data in the NIST Chemistry Webbook, points out that succinic acid exhibits peculiarity in its thermal behavior (either melting or boiling inability). The value of the index for succinic acid is close to zero but marginally positive (3). Thus, in the case of succinic acid, the index is in agreement with the experimentally observed/suspected peculiarity. Similar slightly positive index values are exhibited by malonic acid (number 2 in Table 3), ferulic acid (number 8) and alizarin (number 9). As can be seen in Table 3, for malonic acid in the NIST Chemistry Webbook as for the case of succinic acid, there is lack of boiling data. For ferulic acid and alizarin there is lack of melting and boiling data. Thus, for these substances the index prediction can be considered to be in agreement with the lack of data.

For some other substances, namely, glycine (number 11) as well as some vitamins excluding ascorbic acid (numbers 18–20) and some nonsteroidal anti-inflammatory drugs (numbers 24–28), the value of the index is slightly negative (typically <-30). Compared to the values (e.g., -90) for substances with indisputable melting ability like ethanol, propane etc. (see Table S6), these values are quite higher. In addition, for most of these substances there is either lack of data or reported peculiarities in the NIST Chemistry Webbook. For example, for aspirin a melting point is reported but with rather large uncertainty of $\pm$ 10 K (calculated from 103 out of 110 total measurements). Clearly,

such variation in the melting point is not expected from a substance with melting ability. Thus, for these nine substances (glycine, three vitamins and 5 nonsteroidal anti-inflammatory drugs), the lack of data etc. suggest melting inability, but the index has a negative value and fails to predict the melting inability. However, since the value of the index in these substances is common, in the sense that its value in many cases is close to zero and in general is higher than −30, it can be considered that such negative values can be useful and act as warning. The only exceptions to this seem to be 1,2,3 benzenetriol (number 1 in Table 3) and glycerin (number 62 in Table S6) which exhibit an index value of −3 and −7, respectively, but both melting and boiling data are reported and no evidence for peculiarity in the thermal behavior were detected.

For biomolecules commonly found in essential oils of various plants (numbers 32–38 in Table 3) the index value is highly negative (typically <-65) and thus the index predicts melting ability. Indeed, for six such substances, both melting and boiling data or only boiling data are reported in NIST Chemistry Webbook clearly pointing out that there is no evidence for melting inability in these substances. The seventh natural compound, namely, hypericin (number 38 in Table 3), which is one of the active compounds of Hypericum (Saint John's wort), was not registered in the database of NIST Chemistry Webbook. For this compound, the value of the index is highly positive and thus melting inability is predicted. In other sources e.g., in Material Data Safety Sheets (MSDS) melting point around 320 ℃ is reported. However, in this MSDS [16], in the field of *"Melting/Freezing point"* it is clearly mentioned *"320 ℃ with decomposition"*. Similarly, some antibiotics (number 21–23 in Table 3) were not registered in NIST Chemistry Webbook. The index value for these substances is also highly positive. Instead of benzylpnicillin, the benzylpenicillin potassium salt was registered in NIST and no melting/boiling data are reported. In some MSDS for amoxicillin, some melting points are given while in other MSDS no melting point data are available. Thus, for the case of these three antibiotics (as well as one nonsteroidal anti-inflammatory drug, namely ketorolac)**,** no confirmation or dispute can be claimed.

Other substances with high positive index value are tartaric, citric and caffeic acid (respectively, number 5, 6 and 7 in Table 3), the amino acids arginine and lysine (numbers 12 and 13), various mono- and di-saccharides (numbers 14–16) and ascorbic acid/vitamin C (number 17). For arginine, the two reported melting points exhibit large deviation (see Table 3 for details) while no value for enthalpy of melting (as well as boiling data) are given. For lysine as well as for tartaric acid and caffeic acid, there is a complete lack of melting and boiling data. This is the case also for the vast majority of various carbohydrates (see Table 3). In the few cases of carbohydrates for which melting points are given, again they exhibit rather high deviations. Finally, for vitamin C and citric acid, though some melting point is given, there are no values for enthalpy of melting or boiling data. As for the case of glycine which was mentioned above, it is difficult to accept that the lack of data is because nobody ever bothered to measure the enthalpy of melting of vitamin C or citric acid (both are substances of great interest for the Pharmaceutical and Food Science and Industry). Perhaps it is worth mentioning that for citric acid, in Wikipedia [17], a melting point of 156 ℃ is given and boiling point of 310 ℃ with the comment that it decomposes from 175 ℃ (that is a temperature close to the reported melting point). Thus, for these nine substances, it can be considered that the index correctly predicts the melting inability.

Table 3. *AMI* values for various organic molecular substances. The confirmation/comments are based on the data from the NIST Chemistry Webbook [12], except otherwise noted.

	Substance	$AMI, \frac{kJoule}{mol}$	Confirmation/comments
		miscellaneous (solvents, antioxidants, nutraceuticals etc.)	
1	1,2,3 benzenetriol	−3	Reported melting and boiling data.
2	propanedioic acid (malonic acid)	2	Lack of boiling data.
3	butanedioic acid (succinic acid)	3	Lack of boiling data. Variations in the reported values of melting point have been attributed to decomposition [6].
4	gallic acid	47	Lack of melting and boiling data. Confirmation of melting inability in reference [2].
5	tartaric acid	63	Lack of data for all stereoisomers.
6	citric acid	84	The only data is melting temperature (no value for enthalpy of melting or boiling data).
7	caffeic acid	18	Lack of melting data.
8	ferulic acid	9	For one steroisomer a value for enthalpy of melting is given but no melting point. For the other stereoisomers, there is lack of melting data. For both stereoisomers there is lack of boiling data.
9	alizarin	12	Lack of melting and boiling data.
10	anilin	−53	Reported melting and boiling data.
		amino acids	
11	glycine	−8	Lack of melting and boiling data (only sublimation data).
12	arginine	96	Two melting points with high deviation (498 and 533 K). No enthalpy of melting. Lack of boiling data.
13	lysine	36	Lack of melting and boiling data.
		carbohydrates	
14	hexoses (glucose, fructose, galactose etc.)	75	Glucose: Three different melting points (414, 420 and 423 K). No value for enthalpy of melting. Lack of boiling data. d-mannose: Lack of melting and boiling data. d-galactose: Reported melting point and enthalpy of melting from one source (in which data were obtained from other sources). Lack of boiling data.
15	pentoses (arabinose, xylose etc.)	45	Arabinose and steroisomer: Lack of melting and boiling data. Xylose: For one isomer: Reported melting point and enthalpy of melting from one source (the same as for d-galactose). For other isomers: Lack of melting and boiling data.
16	disaccharides (sucrose, lactose etc.)	210	Sucrose: three melting points (459, 461 and 462 K). Only one point for enthalpy of melting. No boiling data. Lactose: For 6 stereoisomers, lack of melting and boiling data. For 1 stereoisomer (α-lactose) reported melting data. Lack of boiling data.

Continued on next page

	Substance	$AMI, \frac{kJoule}{mol}$	Confirmation/comments
		Vitamins	
17	ascorbic acid (vitamin C)	64	Reported melting point. No value for enthalpy of melting. Lack of boiling data.
18	nicotinic acid (vitamin B3)	−44	Reported melting point and enthalpy of melting. Lack of boiling data.
19	pyridoxine (vitamin B6)	−1	Lack of melting and boiling data.
20	α-tocopherol (vitamin E)	−25	Lack of melting and boiling data.
		Antibiotics	
21	amoxicillin	111	Not registered in NIST.
22	benzylpenicillin	40	Not registered in NIST. For benzylpenicillin potassium salt no melting/boiling data are reported in NIST.
23	levofloxacin	19	Not registered in NIST.
		Nonsteroidal anti-inflammatory drugs	
24	aspirin	−2	Reported melting point and enthalpy of melting. The reported melting point is the average of 103 values and exhibits uncertainty of ±10 K. Lack of boiling data.
25	ibuprofen	−38	Reported melting point and enthalpy of melting. Lack of boiling data.
26	fenoprofen	−15	Lack of melting and boiling data.
27	ketorolac	−16	Not registered in NIST.
28	salicylic acid	−13	Reported melting point and enthalpy of melting. The normal boiling point is not reported-only a reduced pressure boiling point is given.
		Flavonoids	
29	quercetin	103	Reported melting point and enthalpy of melting. This is erroneous and it has been recently clarified [3].
30	sylibin	173	Reported melting point and enthalpy of melting. This is erroneous and it has been recently clarified [1].
31	rutin	341	Lack of melting and boiling data.
		Components of essential oils	
32	thymol/carvacrol	−60	Reported melting and boiling data.
33	eucalyptol	−89	Reported melting and boiling data except for the enthalpy of melting.
34	geraniol	−63	Only boiling data.
35	p-cymene	−90	Reported melting and boiling data.
36	α-terpinene	−94	Only boiling data.
37	cinnamaldehyde	−89	Reported melting and boiling data except for the enthalpy of melting.
38	hypericin	152	Not registered in NIST. Confirmation of decomposition in reference [16].

As a summary, out of 100 substances, the index correctly predicts the melting ability of 68 substances and the melting inability of 17 substances. For 4 substances, no adequate data could be retrieved from a reliable source in order to confirm or dispute the prediction. For 9 substances, there is evidence that suggests melting inability but the index erroneously predicts melting. However, in all

these 9 substances, the value of the index higher than −30 and, in many cases, is close to zero and higher than −10. This points out that the difference for the heat required for melting and decomposition are comparable. Thus, such negative values can be useful to act as warning that there is a chance for melting inability. Finally, 2 substances exhibited similar slightly negative index values but seemingly they exhibit melting ability.

It is worth mentioning that a "holistic" view of the results leads to the following general remarks:

(1) The proposed index predicts melting inability for the vast majority of amino acids. Glycine is one of the simplest amino acids. The index value for glycine was calculated to be equal to −8. As it was discussed, for 9 substances (including glycine), there is evidence for melting inability and the value of the index in all these cases is marginally negative (higher than −30). Calculation of the index for other amino acids (higher molecular weight than the one of glycine) yields positive values. Indeed, in the Handbook of Chemistry and Physics [7], for numerous amino acids (including glycine) and dipeptides, instead of melting point it is mentioned that decomposition occurs e.g., glycine, histidine, alanine, glycyl-glycine, alanyl-glycine and hydroxyphenyl-glycine.

(2) Substances with four or more hydrogen bonded groups, according to the proposed index, are not at all likely to exhibit melting while substances with two or less hydrogen bonded groups are likely to exhibit melting. This can be explained as follows. It is recalled that the number of sites for hydrogen bonding is multiplied by 25 kJ/mol which was considered as the average value of a hydrogen bond. Thus, if more sites for hydrogen bonding are present in the molecule, then the term $0.406 \times \Delta H_{max}$ becomes comparable or higher than 100 kJ/mol (the value for the order of magnitude of a weak chemical bond). If there are four hydrogen bonded groups with an average of three sites, this means that the maximum number of hydrogen bonds is twelve, which, by neglecting any other interactions, corresponds to ΔH_{max} equal to $12 \times 25 = 300$ kJ/mol, that is, the term $0.406 \times \Delta H_{max}$ is higher than 100 kJ/mol (positive index value) by taking into account only the hydrogen bonds.

Various of the above mentioned 9 substances are substances with three hydrogen bonded groups or two hydrogen bonded groups with at least one COOH group. The COOH group contains 5 sites for hydrogen bonding, thus contributing to a greater extent to ΔH_{max} than other hydrogen bonded groups. Thus, the "failure" of the index for these 9 substances may arise from the universal values of the enthalpy of hydrogen bonds and other interactions. In addition, the AMI values close to zero, point out similar (comparable) spontaneity for melting and decomposition. Thus, if more accurate values for ΔH_{max} are used for the implementation of the criterion, then much better approximation would be expected in such marginal cases.

Finally, is should be stressed that the proposed criterion and index yield qualitative information (melting ability or inability) and not quantitative. The primary question that is attempted to be answered is whether a given substance is able to melt or not. If the answer is yes, then the next questions are what is the melting temperature and the heat of fusion. Numerous models exist that can provide quantitative information for these latter questions and accurately predict the melting temperature and heat of fusion. These cannot be interpreted in this study, as that there are methods more accurate than the one used here. Indeed, as mentioned in previous sections, the terms of Eq 5 can be estimated with high accuracy by sophisticated models. However, the novelty of this study is the Eq 5 itself and not the proposition of a method for predicting heat of fusion. In few words, the question "is able a substance to melt" and the questions "what is the melting point or the heat of fusion of a substance" are distinct questions. Thus, the comparison with such methods is rather pointless, simply because the available models and the proposed criterion try to answer a different question.

4. Conclusions

The entropy change upon decomposition is expected to be higher than the respective one upon melting. Consequently, from an entropy point of view, the change of Gibbs free energy tends to be more negative for decomposition than for melting. Of course, the change of Gibbs free energy is affected also by the enthalpy changes during melting and decomposition. From this point of view, melting is thermodynamically favored over decomposition. It is likely that the enthalpy values for melting and decomposition are comparable, in cases where either the enthalpy for decomposition is low e.g., presence of weak chemical bonds, or the enthalpy of melting is high due to increased number of strong intermolecular interactions. In such a case, it is likely that decomposition will be thermodynamically favored over melting and thus the substance will exhibit melting inability. Also, it must be taken into account that regarding melting ability/inability, the extent of decomposition is not important. For this reason, the comparison of enthalpy of melting and decomposition can be performed on the basis of intermolecular interactions and strength of the weakest chemical bond. The proposed criterion/index takes into account all the above.

The parameters of the criterion can be calculated theoretically through statistical thermodynamics etc. Here, instead, a very simple method was developed that allows for rapid and massive implementation of the criterion/index. The estimation of the value of the index is based partially on a very simple group contribution method and partially on a distorted version of Trouton's rule. Despite its simplicity, the proposed methodology yields fairly acceptable approximate predictions for the exhibition of melting ability and inability by various organic substances. Slightly negative index values imply little difference between enthalpy for melting and decomposition, thus, in such cases, the index can act as a warning.

Substances with three groups able to form hydrogen bonds e.g., OH groups, are marginally likely to exhibit melting. If one of these such groups is COOH, which has a maximum of 5 sites for hydrogen bonds, then the probability for melting inability increases. Substances with 4 or more such groups are very likely to exhibit melting inability. The lack of melting/boiling data for various common substances of great scientific and industrial interest, such as amino acids, carbohydrates etc. matches the index's predictions (either positive values or slightly negative values) and seems to be related to the melting inability of such substances.

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References

1. Tsioptsias C, Spartali C, Marras SI, et al. (2022) Thermochemical transition in low molecular weight substances: The example of the silybin flavonoid. *Molecules* 27: 6345. https://doi.org/10.3390/molecules27196345

2. Tsioptsias C, Tsivintzelis I (2022) Insights on thermodynamic thermal properties and infrared spectroscopic band assignments of gallic acid. *J Pharm Biomed Anal* 221: 115065. https://doi.org/10.1016/j.jpba.2022.115065

3. Tsioptsias C, Tsivintzelis I (2022) On the thermodynamic thermal properties of quercetin and similar pharmaceuticals. *Molecules* 27: 6630. https://doi.org/10.3390/molecules27196630

4. da Costa EM, Filho JMB, do Nascimento TG, et al. (2002) Thermal characterization of the quercetin and rutin flavonoids. *Thermochim Acta* 392–393: 79–84. https://doi.org/10.1016/S0040-6031(02)00087-4

5. Galwey AK, Laverty GM (1993) The thermal decomposition of dehydrated d-lithium potassium tartrate monohydrate: Molecular modification by a homogeneous melt mechanism. *Proc R Soc Lond A* 440: 77–93. https://doi.org/10.1098/rspa.1993.0005

6. Wilhoit RC, Chao J, Hall KR (1985) Thermodynamic properties of key organic oxygen compounds in the carbon range C_1 to C_4. Part 1. Properties of condensed phases. *J Phys Chem Ref Data* 14: 1–175. https://doi.org/10.1063/1.555747

7. Haynes WM (2004) Standard thermodynamic properties of chemical substances, In: Haynes WM, *CRC Handbook of Chemistry and Physics*, Boca Raton: CRC Press.

8. Earle MJ, Esperança JMSS, Gilea MA, et al. (2006) The distillation and volatility of ionic liquids. *Nature* 439: 831–834. https://doi.org/10.1038/nature04451

9. Stuart B (2004) *Infrared Spectroscopy: Fundamentals and Applications*, England: John Wiley and Sons Ltd.

10. Tsivintzelis I, Kontogeorgis GM, Panayiotou C (2017) Dimerization of carboxylic acids: An equation of state approach. *J Phys Chem B* 121: 2153–2163. https://doi.org/10.1021/acs.jpcb.6b10652

11. Sinnokrot MO, Valeev EF, Sherrill CD (2002) Estimates of the Ab initio limit for $\pi-\pi$ interactions: The benzene dimer. *J Am Chem Soc* 124: 10887–10893. https://doi.org/10.1021/ja025896h

12. NIST Chemistry WebBook. National Institute of Standards and Technology, 2003. Available from: https://webbook.nist.gov/.

13. Zumdahl SS, Zumdahl SA, DeCoste DJ (2018) *Chemistry*, Boston: Cengage Learning.

14. Atkins PW, De Paula J, Keeler J (2018) *Atkins' Physical Chemistry*, New York: Oxford University Press.

15. Trouton F (1884) IV. On molecular latent heat. *Lond Edinb Dubl Phil Mag* 18: 54–57. https://doi.org/10.1080/14786448408627563

16. FERMENTEK Hypericin Safety Data Sheet. Available from: https://www.fermentek.com/sites/default/files/Hypericin%20SDS.pdf.

17. Wikipedia Citric acid. Available from: https://en.wikipedia.org/wiki/Citric_acid.