Entropy–enthalpy compensation in the fusion of organic molecules: implications for Walden's rule and molecular freedom in the liquid state

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Abstract

Using a literature compilation of melting point and fusion enthalpy data from over 700 organic compounds it is shown that the entropy of fusion, ΔS_f, is dependent upon the enthalpy of fusion, ΔH_f. 'Flexible' molecules (those that are potentially multi-conformational) tend to yield higher values of ΔS_f for a given ΔH_f, than do 'rigid' ones.

The overall dependency is roughly linear and gives a positive intercept on the entropy axis. This is identified with ΔS_{to}, the entropy gained from onset of translational and orientational freedom on melting. The enthalpy dependent component, ΔS_h, is considered to arise by analogy with entropy–enthalpy compensation in ligand binding processes.

Because of the way the ΔH_f distribution is truncated in typical 'random' selections of chemical compounds, dependency inevitably leads to kurtosis of the ΔS_f value distribution and this is augmented by kurtosis in ΔH_f and molecular weight. These are the main reasons for the often observed 'constancy' of ΔS_f for 'rigid' molecules which is termed Walden's Rule. This rule has therefore no general validity.

'Flexible' molecules usually possess additional entropy, ΔS_c, from the release of conformational disorder in the melt. Their relative position on the $\Delta S_f/\Delta H_f$ plot can indicate the magnitude and extent of such disorder. For instance the situation of n-alkanes suggests relative conformational freedom but n-alkyl theophyllines appear to be constrained.

Molecules with strongly hydrogen bonding groups (donor and acceptor),even with n-alkyl groups, have lower relative ΔS_f, presumably due to association. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

The entropy of fusion, ΔS_f, is related to the melting point, MP, and the enthalpy of fusion, ΔH_f, according to the simple thermodynamic relationship

$$\Delta S_f = \Delta H_f / MP. \qquad (1)$$

Both ΔH_f and MP can be determined experimentally and thus values for ΔS_f can be readily obtained.

Simple theory and inspection of ΔH_f data from organic compounds suggests that they should be, and are, determined by simple group additivity, whereby the various molecular components contribute in a linear and characteristic manner to the total value. However no exact relationship can be expected as different molecules will align and position their com-

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ponent parts in different ways in the solid, so that individual group contributions will vary depending on the particular case.

Inspection of melting point tables suggests that group additivity is also relevant for MP as well, but only for rigid molecules.

There has thus been little surprise in claims that, based on observation, ΔS_f for non-spherical rigid molecules is roughly constant at around 50–60 J K^{-1} mol^{-1}. This is termed Walden's Rule. This author found [1] 35 compounds, that did not associate in the liquid state, to have an average ΔS_f of 13.5 entropy units 'eu.' (56.5 J K^{-1} mol^{-1}).

Roughly spherical molecules are not bound by the rule because they often yield anomalously low values for ΔS_f. Neither are flexible molecules, with elements of structure that can assume different conformations in the liquid phase, but which are frozen into only one in the solid. The latter would be expected to possess higher values of ΔS_f.

These simple precepts have been the basis, for instance, of a prediction scheme [2] that used Walden's constant with additional increments of 2.5 eu. ($\sim$10.5 J K^{-1} mol^{-1}) for each extra non-hydrogen atom over five in a flexible chain. The predicted values were applied to the problem of estimating the solubilities of pharmaceutical compounds.

Another problem in pharmaceutics relates to the binding of ligands to large protein molecules such as enzymes or receptors. A significant part of the energetics is concerned with the amount of translational and rotational entropy lost when a relatively free ligand in solution is attached to a macromolecule.

It has been estimated [3] that when two small molecules come together in solution to form a tight covalent bond, the entropy of binding, ΔS_b, is of the order of -196.7 J K^{-1} mol^{-1} at 298 K. This is based on treating the solute molecules as having the freedom of the gas phase though this is doubtful and the real figure is probably rather smaller [4]. It was also pointed out [3] that weak binding to form a relatively 'loose' complex will preserve some of the translational and rotational motion of the individual constituents as low frequency vibrational modes which should possess significant amounts of entropy. This would make ΔS_b considerably less negative and suggests that there is some correlation between the enthalpy of binding, ΔH_b, and ΔS_b. This effect, termed

'enthalpy–entropy compensation', has recently received detailed theoretical and experimental study [5,6] though alternative explanations, involving intrinsic properties of the solvent, are sometimes given, in particular for drug/receptor binding [7,8].

The weak intermolecular forces that mediate the binding of ligands to macromolecules are of the same type and order of magnitude as those involved in crystallisation. The ligand binding process may therefore be an appropriate exemplar. By analogy it might thus be expected that ΔS_f is also dependent on ΔH_f. This would be contrary to Walden's Rule.

Theoretical treatments of ΔS_f are hampered by uncertainties surrounding the liquid state. Early work, for example [9], regarded it more as a highly compressed gas with the molecules enjoying a large degree of translational and orientational freedom. Experimental data over the years however has demonstrated that liquids generally possess considerable short range order. Unfortunately the liquid state is not particularly amenable to probing by using the entropy of vapourization as this is dominated by the volume increase (viz. Trouton's constant) except where there is gross association from interactions like hydrogen bonding.

A number of studies [10–12] have concentrated on finding the contribution to ΔS_f from the conformational freedom (i.e. increase in disorder) that certain flexible molecules (alkanes) can gain on melting. This has involved elucidating the other contributions to the total entropy change usually regarded as being made up of a lesser part from release of translational disorder (the so-called communal entropy) and a greater part from the volume expansion. While the conformational entropy can sometimes be estimated from spectroscopic measurements the other contributions cannot and there is little agreement on the size or even the mechanism of the others.

Strangely, there seems to have been little study of whether there is a relation between ΔS_f and ΔH_f as suggested by analogy with considerations on ligand binding. Fortunately two extensive compilations of the ΔH_f and MP values of a wide range of organic compounds have recently been made by Acree [13,14]. These enable a detailed study to be made of the relationships between the thermodynamic parameters and with molecular structure, which is presented below.

2. The data and its preliminary analysis

The information [13,14], taken from the literature, consists of measured melting enthalpies and melting points (in °C) for over 700 organic molecules, mainly non- or weak electrolytes. There is some duplication, so for on the purposes of this work, multiple values for any compound have been averaged. There is one salt and this and one other compound, chloropicrin, which appears to possess an anomalously high ΔH_f, have been arbitrarily eliminated from the data set to give a total of 739 compounds with values of ΔS_f calculated using Eq. (1). Temperatures were converted to absolute by addition of 273.2. Acree's caveat [13,14] is echoed here in that in a compilation of this size one or two transcription errors may arise.

Fig. 1 is a histogram of the ΔS_f values which appear to divide into three groups.

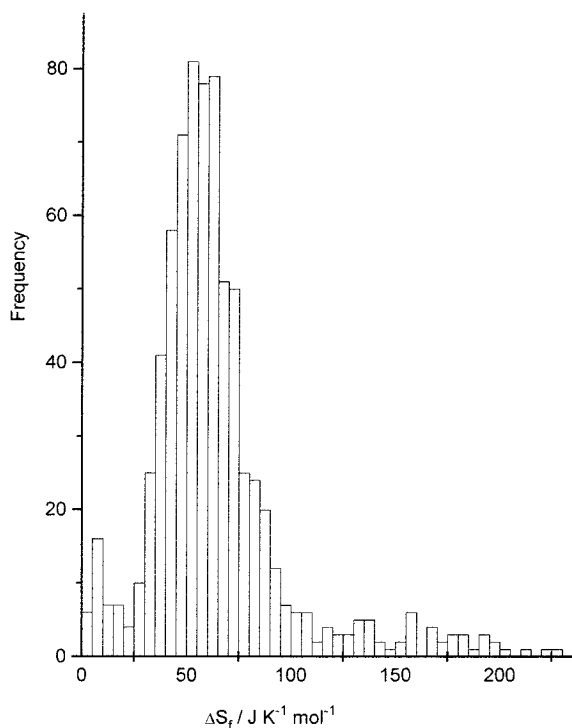Firstly, there are a number of compounds with unusually small values for ΔS_f i.e., less than $\sim$20 J K^{-1} mol^{-1}. These compounds are not obviously distinguished by chemical structure or MP though their ΔH_f values are also smaller than average.

Secondly, the majority of values are clustered in a peak between 20 and 110 J K^{-1} mol^{-1} and finally there is a long tail to higher values, i.e. greater than $\sim$110 J K^{-1} mol^{-1}. This latter distribution is almost entirely represented by compounds having long flexible (methylene) chains.

In order to try to differentiate the contributions from conformational disorder the dataset has been divided in two, 'rigid' and 'flexible', meaning mono- and multi-conformational, respectively. The essential qualification for flexibility is more than three consecutive singly bonded non-hydrogen atoms in a non-cyclic chain, more than four in a cyclic system and more than one as a ring substituent.

There is considerable uncertainty however, whether all potentially flexible units will be disordered in the liquid phase and to what extent. While the long methylene chains of the *n*-alkanes are well known [10–12] to take up a variety of conformations in the liquid state it is by no means certain that, for example, many substituent groups on aromatic rings would do so. In the event some assignments here are arbitrary with, usually, all potential flexibles going into the second subset. However amino and nitro substituents on aromatic rings are considered to be fixed (due to conjugation) and there are also some other instances where conformational freedom might be restricted.

Fig. 2a shows ΔS_f plotted against ΔH_f for the entire set of 739 compounds with the subsets distinguished. There are 358 'rigids' and 381 'flexibles'. The most striking feature is the apparently strong relation between ΔS_f and ΔH_f, with the 'flexible' molecules tending to yield higher values of ΔS_f for a given ΔH_f.

The overall trends are roughly linear but there is a change in slope at very roughly $\Delta S_f = 20$ J K^{-1} mol^{-1}/ $\Delta H_f = 5000$ J mol^{-1}. This can be seen more clearly in Fig. 2b where just the 'rigids' are plotted. The great mass of the 'rigids' and various 'flexible' chemical series, all with $\Delta S_f > 20$ J K^{-1} mol^{-1}, extrapolate to give positive intercepts on the entropy axis. The relationship is therefore of the type $\Delta S_f = A + B\Delta H_f$ (*A* and *B* being constants) and reflects the rising trend of MP as ΔH_f (and molecular weight) increase.
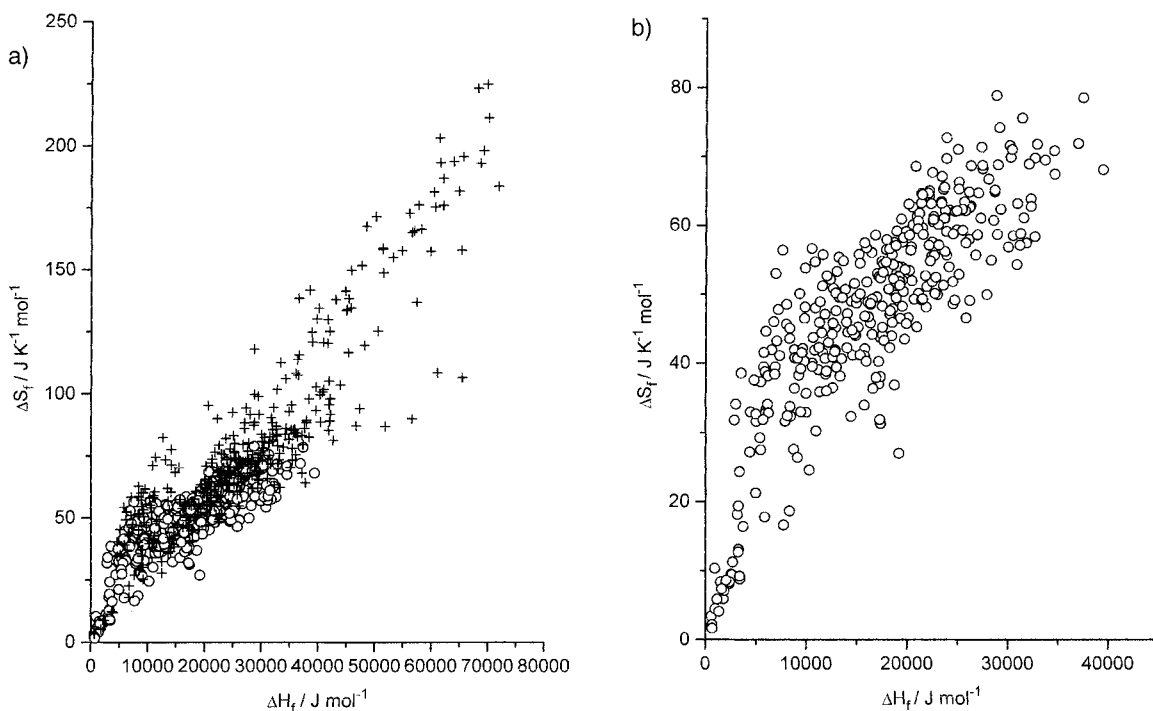

Fig. 1. Histogram of ΔS_f values for the entire set of 739 compounds.

Fig. 2. (a) Plot of ΔS_f against ΔH_f for the entire set of 739 compounds: 'rigids', $\bigcirc$; 'flexibles', +. (b) Plot of ΔS_f against ΔH_f for the 358 'rigids'.

Below the discontinuity the data is on a steeper line that goes nearly through the origin but there is significant scatter so that MP is not constant.

In general the subset attribution appears to be correct. For instance the 'rigid' set contains 101 members that are definitely mono-conformational such as benzene rings with halogen substituents. These compounds are fairly well distributed (not shown) throughout the 'rigids' though on a slightly steeper line.

The group with ΔS_f values below $\sim$20 J K^{-1} mol^{-1} contains several examples of roughly spherical molecules such as cyclo-hexane and tri-*t*-butyl alcohol. Such types of molecules are often in plastic crystal form near to and at the MP after undergoing solid–solid phase transitions [15,16] and thus possess considerable orientational disorder in the solid state. A non-spherical example in this group is succinonitrile which is also known to be a plastic crystal [17]. No other sort are likely to have ΔH_f values below 5000 J mol^{-1} except for very small molecules not in the Acree compilation.

3. The 'rigid' set and Walden's Rule

Fig. 3(a–c) are histograms of ΔS_f, ΔH_f and molecular weight, MW, but without compounds having $\Delta S_f < 20$ J K^{-1} mol^{-1} ($N = 331$). Walden's Rule appears to be obeyed to the extent that the entropy values are gathered in a relatively narrow peak having a mean value of $\Delta S_f = 50.92$ J K^{-1} mol^{-1} with a width in the distribution of 22.38 J K^{-1} mol^{-1} (two standard deviations). It is evident however that the ΔH_f and MW data is also severely kurtosed as well.

In the case of the MWs this is not unexpected. The peak of the MW distribution (Fig. 3c) is between 150 and 175 daltons and a cursory study of the formula index of organic compounds in, for instance, any edition of the CRC Handbook of Chemistry and Physics (The Rubber Handbook) shows a similar peaked distribution. This is quite understandable because as MW rises the number of possible isomers rises also, but increasing size and complexity eventually reduces the number of compounds (in any MW interval) that are in existence because of increased
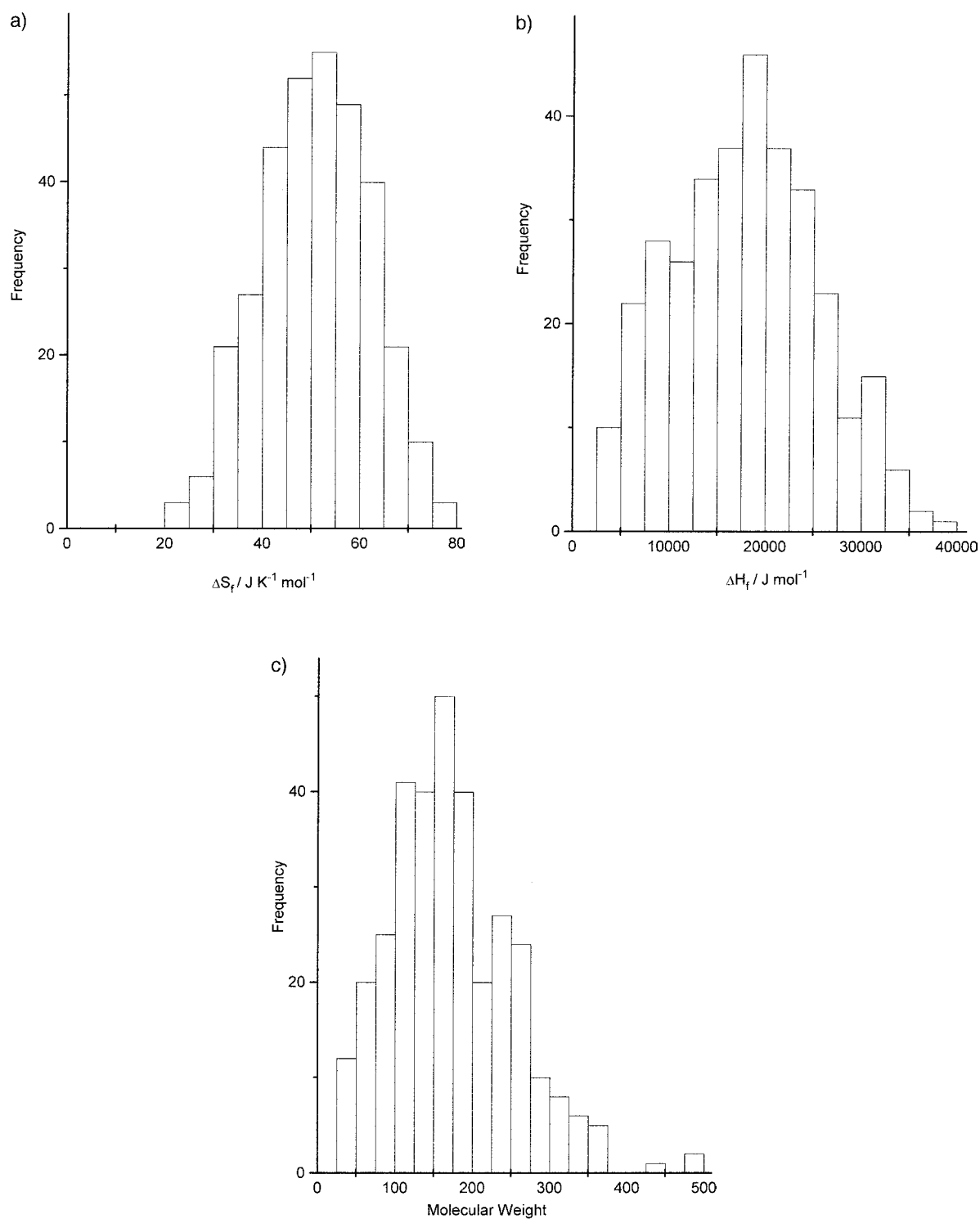
Fig. 3. Histograms of (a) ΔS_f, (b) ΔH_f, (c) MW values for the 'rigid' set, excepting compounds with $\Delta S_f < 20 \, \text{J K}^{-1} \, \text{mol}^{-1}$.

difficulties with chemical synthesis, stability etc. Thus any random selection from the set of known compounds will be kurtosed in this manner.

As ΔH_f is crudely dependent on MW (owing to group additivity) and thus kurtosed as well, and ΔS_f evidently dependent in turn on ΔH_f (Fig. 2) then it might be concluded that the rough constancy of ΔS_f is merely a consequence of the way in which the data in this and possibly any other randomly selected set of 'rigid' compounds is distributed. This is not however the whole story.

Fig. 4a shows all 331 compounds ($\Delta S_f > 20$ J K^{-1} mol^{-1}) in the data set arranged in cells, 5 J K^{-1} mol^{-1} entropy and 2500 J mol^{-1} enthalpy units to a side, the numbers of compounds in each cell being shown. It can be seen that the peak in ΔS_f arises in part due to the way the data set is truncated in the enthalpy axis so that the occupied lengths of rows either side of the central one (row 7) are progressively cut back. If the data set could be extended to higher and higher ΔH_f, and the relation between ΔS_f and ΔH_f continued to hold, then the distribution in the former would become increasingly broad and flat topped and its apparent constancy would vanish. This is demonstrated in diagrammatic form in Fig. 4b.

In addition of course the kurtosis in MW and ΔH_f evidently feeds through as well, by adding to the middle of the central rows (Fig. 4a).

Walden's Rule is therefore not a universal law but merely an artifact of the way that any randomly selected set of compounds will tend to be distributed in MW space.

4. Discussion

As shown above ΔS_f is evidently correlated with ΔH_f but this relationship does not seem to have been explicitly studied before. For instance at least one plot of ΔH_f versus ΔS_f for a limited number of compounds has been given previously [18] but the MPs were deliberately chosen to be quite similar (to force a linear relationship), the aim being only to demonstrate the wide range of enthalpy/entropy values that give rise to similar melting temperatures.

A plausible explanation for dependency of ΔS_f on ΔH_f can be given which follows previous speculation [3] on binding entropies.

The higher the enthalpy change on melting, the tighter the association of the molecules in the solid state and therefore the higher the frequencies of the vibrational modes (stretches and torsions) associated with the intermolecular (non-covalent) bonds that are formed. The higher the frequency of a vibrational mode, the lower the partition function and therefore the entropy. However unlike the ligand binding picture the molecules would still be loosely bound to one another in the liquid state but with much lower intermolecular vibrational frequencies possessing therefore rather greater entropy. Thus the greater ΔH_f the more entropy that will be gained on melting.

For ligand binding the entropy term tends to a maximum and the relation with ΔH_b is curved [5,6]. This would also be expected for melting but there is no obvious curvature in the fusion data plot (Fig. 2a and b). It may be that this is only observable at higher values of ΔH_f such as those presented by the metallic elements (see below, Fig. 6).

Not all of ΔS_f is necessarily enthalpy dependent. Apart from any conformational entropy, ΔS_c, in flexible molecules, it is likely that there will be a component, denoted here as ΔS_{to}, independent of the magnitude of ΔH_f, which derives from the gain in overall translational and orientational freedom on melting. Though of course molecules in the liquid are still bound to one another (the melt is not a gas) any particular bond is transient and ΔS_{to} might be looked upon as being related to the probability of a molecule re-orienting or leaving its immediate surroundings. Such a process would be a function of the liquid state only and not governed by the forces present in the crystal; i.e it would be independent of ΔH_f.

The entropy of fusion might therefore be regarded as being made up as follows.

$$\Delta S_f = \Delta S_h + \Delta S_{to}(+\Delta S_c). \qquad (2)$$

Alternatively some treatments of the subject [10–12] give:

$$\Delta S_f = \Delta S_v + \Delta S_{to}(+\Delta S_c), \qquad (3)$$

where ΔS_v is derived from a volume expansion term and presumably corresponds to ΔS_h in (2). Clearly expansion would require an energy input but the situation is complicated in that one or two solids (e.g. water) contract on melting, yet still possess a

a)
Row no	ΔS$_f$ range J K^{-1}mol^{-1}	Frequency per Cell															Row total
12	75–80	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	3
11	70–75	0	0	0	0	0	0	0	0	2	1	1	3	2	1	0	10
10	65–70	0	0	0	0	0	0	0	3	4	5	4	1	3	0	1	21
9	60–65	0	0	0	0	0	0	1	12	12	9	2	4	0	0	0	40
8	55–60	0	0	1	2	1	6	10	9	7	5	2	5	1	0	0	49
7	50–55	0	1	2	4	7	7	18	7	6	1	1	1	0	0	0	55
6	45–50	0	2	5	4	11	10	10	6	2	2	0	0	0	0	0	52
5	40–45	0	5	8	8	11	7	5	0	0	0	0	0	0	0	0	44
4	35–40	3	6	4	6	3	4	1	0	0	0	0	0	0	0	0	27
3	30–35	4	6	6	1	1	3	0	0	0	0	0	0	0	0	0	21
2	25–30	1	2	2	0	0	0	1	0	0	0	0	0	0	0	0	6
1	20–25	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	3

ΔH$_f$ range: first column:- 2500–5000 J.mol^{-1}
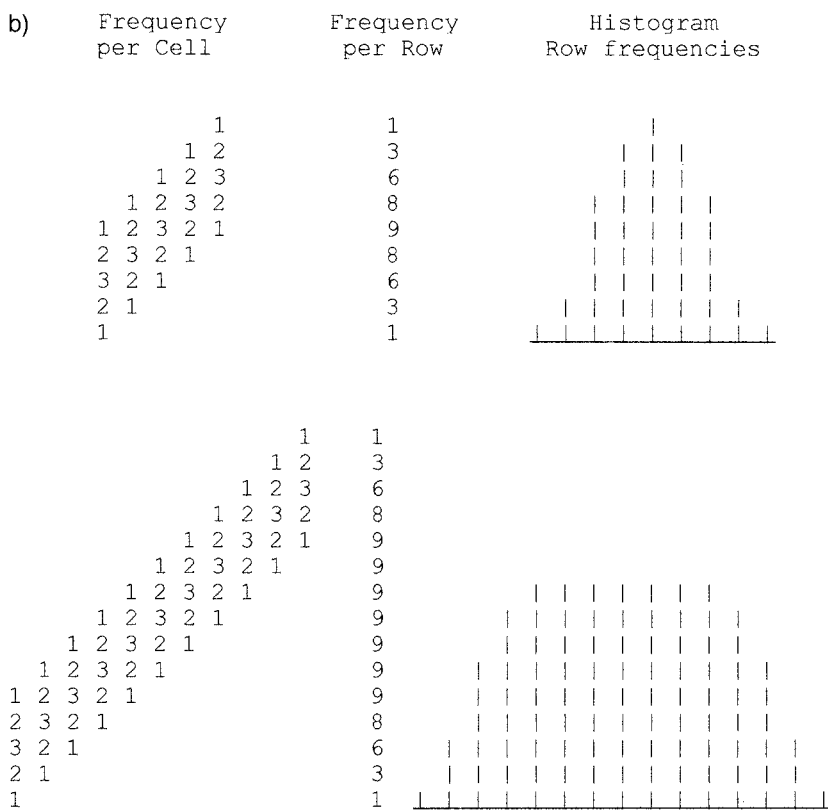last column:- 37500–40000 J.mol^{-1}

b)

Fig. 4. (a) ΔS$_f$/ΔH$_f$ cell frequencies for the 331 compounds in the 'rigid' set (excepting compounds with ΔS$_f$ < 20 J K^{-1} mol^{-1}) to show how the central row (No. 7) has the maximum frequency to dominate the average value of ΔS$_f$; (b) ΔS$_f$/ΔH$_f$ cell frequencies for two hypothetical sets with different truncation in the ΔH$_f$ (horizontal) axis where ΔS$_f$ is linearly dependent on ΔH$_f$ with a triangular spread (1, 2, 3, 2, 1 variation along the column). The central rows inevitably hold the largest frequency of compounds. The effect is the same even if the spread is boxcar (i.e., frequency is 1, 1, 1, 1, 1). Note that any kurtosis in ΔH$_f$ that feeds through into ΔS$_f$ will add to the occupancy of the central rows.

significant positive ΔH_f. Estimating ΔS_v appears to be fraught with difficulty, apparently because of the need to extrapolate pressure variable data [10,12], and there is no agreement even on studies of the same compounds.

Can Eq. (2) therefore shed more light on the problem, in particular the magnitude of ΔS_{to}?

Linear regression on the 331 'rigids' (all $\Delta S_f > 20$ J mol^{-1} K^{-1}) yields a correlation coefficient (R^2) of 0.64.

$$\Delta S_f = 29.67(0.951) + 0.00119\Delta H_f(0.00005), \quad (4)$$

SD = 6.722 J K^{-1} mol^{-1}. Figures in brackets denote the standard errors on the coefficients and SD the standard deviation.

An obvious tactic is to identify the intercept at just less than 30 J K^{-1} mol^{-1} with ΔS_{to}. This will of course represent an average for molecules with three degrees of potential orientational freedom (and translational freedom). Linear molecules (two degrees of orientational freedom along with translational free-

dom) or single atoms (just translational freedom) should yield values less than this. This implication can be tested by examining the relevant data. Figs. 5 and 6 show plots for a selection of data taken from the literature [19].

Linear regression on 17 linear molecules (Fig. 5) gives an intercept of 10.5 J K^{-1} mol^{-1}. Fig. 6 is a plot of data from 54 elements thought to be single atoms, unassociated in the liquid state (i.e., excluding Periodic Table groups 1A, 2B, 3A, 4A, 5A, 6A, 7A). They yield an intercept of about 2 or 5 J K^{-1} mol^{-1} depending on whether the line is considered to be curved or not. Confusingly there are four outliers, all noble gases, with very low ΔH_f but ΔS_f values of around about 12 J K^{-1} mol^{-1}.

It is heartening to see that these numbers are at least in expected rank order and if they are meaningful and indeed represent ΔS_{to} suggest that a greater part of this term comes from orientational disorder. In passing it should be noted that the precise values must not be taken too literally, despite the small standard errors given by the regression analysis. For example in the
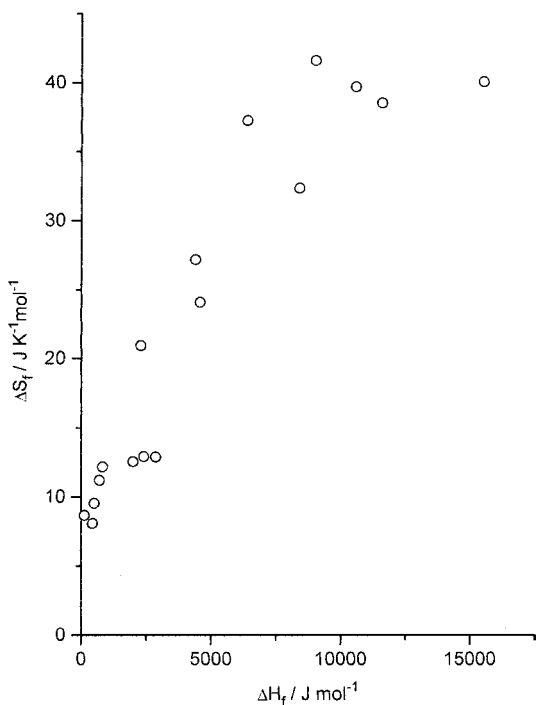

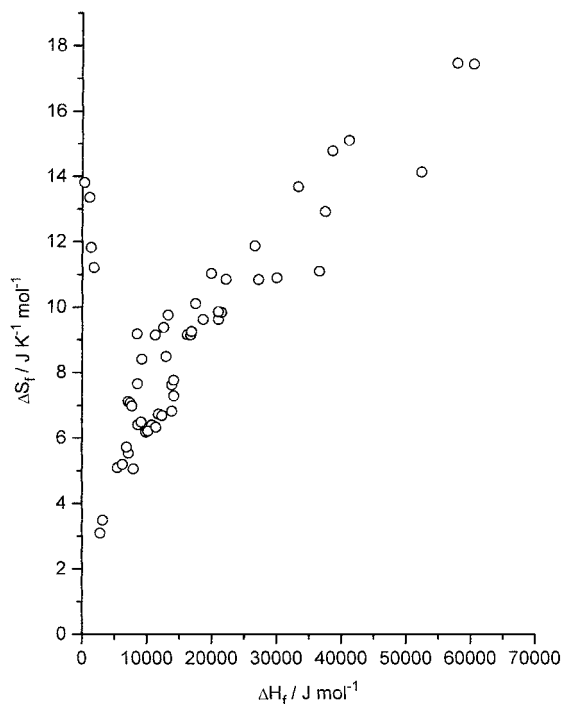Fig. 5. Plot of ΔS_f against ΔH_f for 17 linear molecules.

Fig. 6. Plot of ΔS_f against ΔH_f for 54 elements (all metals except for Ne, Ar, Kr, Xe).
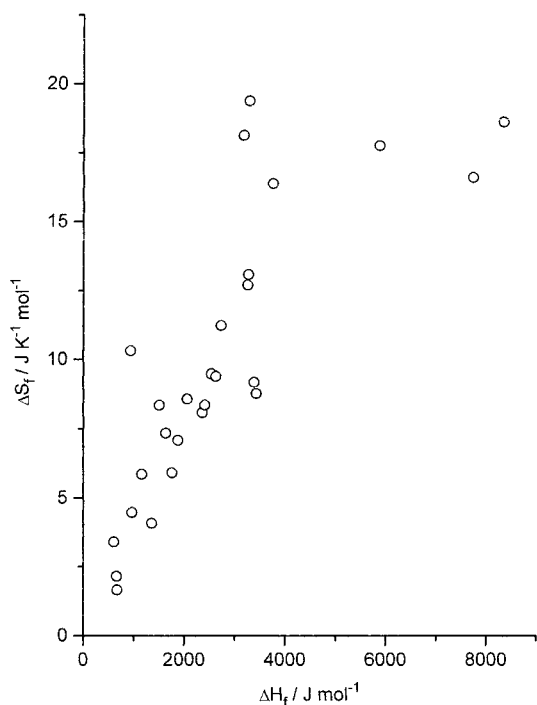
Fig. 7. Plot of ΔS_f against ΔH_f for the 'rigid' compounds with $\Delta S_f < 20$ J K^{-1} mol^{-1}.
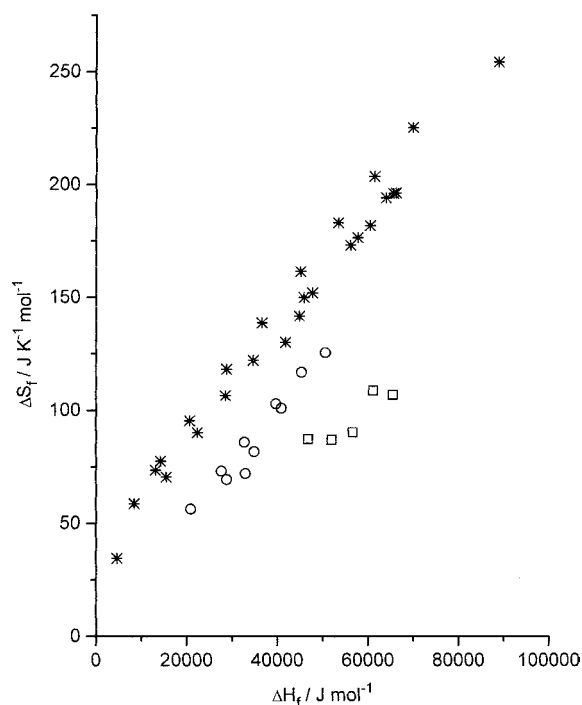

Fig. 8. Plot of ΔS_f against ΔH_f for 'flexible' compounds: n-alkanes, ★; n-alkane dicarboxylic acids, ○; 4,4'-dicarboxylic-diphenoxy alkanes, □.

case of the 331 'rigids', the correlation being what it is, the intercept is somewhat lifted over what it would be if the data was eye-balled.

Finally the data from the 'rigid' set that have $\Delta S_f < 20$ J K^{-1} mol^{-1} can be considered. The plot is shown in Fig. 7. Linear regression gives an intercept of only about 4 J K^{-1} mol^{-1} while eye-balling the smaller data values puts a line through the origin. Many if not all of the molecules represented here are in the form of plastic crystals and so are already disordered to an extent before melting.

With a high degree of freedom (disorder) in plastic phases, a low value for ΔS_{to} is to be anticipated but there is no reason why it should be the same for all these compounds as the type and extent of disorder will be variable. Thus it is not clear why these data are not more spread out.

4.1. Molecules with unbranched alkane chains

Fig. 8 shows three series of flexible molecules. The alkane series data has been augmented with additional compounds from the literature [20,21]. Each series appears to have a separate linear relationship between ΔS_f and ΔH_f but the latter values are not in general, sequential with methylene number.

Because of the extra ΔS_c term these compounds might be anticipated to lie above the mass of the 'rigids' in the $\Delta S_f/\Delta H_f$ plot but while the alkanes and some others do so, this is not the case for the n-alkane di-carboxylic acids and the 4,4'-dicarboxylic acid-diphenoxy alkanes. The carboxylic acids seem highly likely to be considerably associated in the melt owing to strong intermolecular hydrogen bonding with consequent reduction in total entropy. This mechanism has in fact already been proposed for the dicarboxy-diphenoxy alkanes [22].

The n-alkanes have been the subject of some attention [10–12]. Their situation is complicated by the fact that, neglecting the very small ones, only those with C numbers 4, 5 and even 6–20 are not known to have solid–solid phase transitions. The others exhibit quite significant amounts of both enthalpy and entropy change, to give plastic crystals. Most commonly a

so-called 'rotator' phase is in being prior to melting. These transitions are the cause of the lack of sequence matching of ΔH_f with carbon number.

If the regression line for the 331 'rigids' (Eq. (4)) is taken as representative of $\Delta S_h + \Delta S_{to}$ for the *n*-alkanes as well, then subtraction from their ΔS_f values should give ΔS_c. Dividing them into two groups, I and II, i.e., those with and without plastic phases, respectively, yields fitted average values for $\Delta S_c/M$ of 6.94 J K^{-1} mol^{-1} for I and 3.54 J K^{-1} mol^{-1} for II. Group I have carbon numbers 4, 5, and even 6–20 while group II are odd 7–15, 19, odd 21–29 and 36. M here is the number of conformational elements that can contribute to ΔS_c; it is three less than the carbon number.

While these numbers are at least within the theoretical maximum of 9.136 J K^{-1} mol^{-1} (=$R \ln Q$, where R is the gas constant and Q the partition function) for rotatable units with three equally possible conformations ($Q = 3$), they are bigger than what would be expected. This is because the gauche conformers are higher in energy than the *trans* form by 2100 J mol^{-1} or more [23]. This means that the partition function is rather less than 3 and $\Delta S_c/M$ for butane calculates out at only 2.24 J K^{-1} mol^{-1} with slowly rising values for the higher homologues as the MPs increase. The rising trend is slightly damped as gauche/gauche combinations are higher still in energy terms and certain are forbidden due to steric clashes.

Nevertheless using the $\Delta S_f/\Delta H_f$ relation does give figures for $\Delta S_c/M$ that are in the right vicinity though higher than they ought to be.Finally it is of interest to get a value for ΔS_{to} for the solid–solid transition to the rotator phase. This phase is essentially characterised by free rotation about the long axis. Combining data from two sources [20,21] provides data on group II and linear regression yields an intercept of 10.0 J K^{-1} mol^{-1}. This is, as should be expected, about a third of the value of the intercept for the 'rigids' and is another indication that orientational disorder is the major contributor to ΔS_{to}.

4.2. Chemical structure effects on ΔS_f

With over 300 compounds in the 'rigid' set, it is possible to get a crude idea of some of the effects of structure by regression analysis. As this game can be played 'ad-infinitum' just one combination is tested here. Indicator variables F and HB are used to designate aromatic 'flatness' and strong H-bonding, respectively, F is either 0 or 1 but HB denotes the number of strong H-bonding groups and takes the values 0, 1 or 2. Assignment is somewhat arbitrary, where certain aromatics have large substituents, F is put to zero. Strong H-bonders are regarded as carboxylic acids and ureas but not alcohols and the molecules must obviously possess the capacity to both accept and donate. Such assignments yield the following:

$$\Delta S_f = 30.78(0.999) + 0.0014\Delta H_f(0.00006)$$
$$-0.0166MW(0.0058) - 5.408HB(1.16)$$
$$-2.18F(0.783), \qquad (5)$$

SD = 6.44 J K^{-1} mol^{-1}.

This result demonstrates that in the same way as the dicarboxylic acid alkanes, hydrogen bonding has a negative effect and so also does MW. Aromatic 'flatness' also appears to reduce ΔS_f but whether this is due to association by a stacking effect in the liquid or perhaps disorder in the crystal (many such compounds are known to form plastic phases in the solid [15]), or both, cannot be established.

4.3. Using the $\Delta S_f/\Delta H_f$ relation to ascertain conformational disorder

Fig. 9 shows data from 3-(*n*-alkyloxy)-1,2 propanediols, 2-amino-4-(*N*-alkylanilino)-6-isopropenyl 1,3,5 triazines and 8-*n*-alkyl-theophyllines. Also displayed is the regression line (Eq. (4)) that defines the 'rigids'. It is evident that the first two series lie along a steeper gradient in a similar fashion to the *n*-alkanes, indicating that the alkyl chains are multi-conformational in the liquid and therefore contribute towards ΔS_f. The theophyllines, however, lie along the 'rigid' line suggesting that for these particular compounds the chains remain conformationally restricted in the melt.

The three theophyllines that have $\Delta H_f < 30000$ J mol^{-1} actually yield solid–solid transitions which clouds the issue, though it is interesting that they remain on the line. If they were to be somewhat disordered prior to melting the expectation would be that they should be on a lower line with a smaller intercept. However it is not strictly necessary
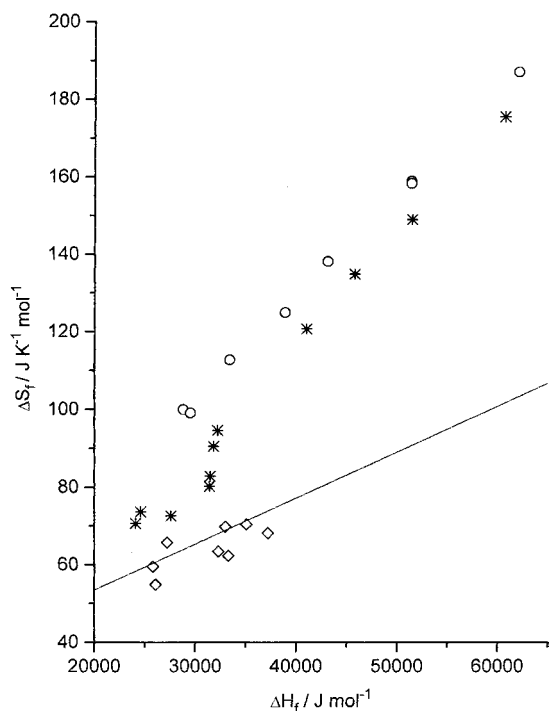
Fig. 9. Plot of ΔS_f against ΔH_f for 'flexible' compounds: 3-(n-alkyloxy)-1,2 propanediols, $\bigcirc$; 2-amino-4-(N-alkylanilino)-6-isopropenyl 1,3,5 triazines, $\bigstar$; 8-n-alkyl-theophyllines, $\diamondsuit$.

for a solid state phase transition to result in loss of order.

Another class of compounds, which to be on the safe side for the 'rigids' analyses above, were designated as 'flexibles', are carbomethoxy substituted benzenes and naphthalenes. While it could be imagined that singly or para disubstituted members might exhibit multiple conformations, heavily substituted examples would seem likely to suffer from steric hindrance. On the $\Delta S_f/\Delta H_f$ plot they cluster (not shown) to form a continuation of the general mass of the 'rigids' so in the absence of any strong hydrogen bonding to bring down ΔS_f (the flatness effect, if any, will be small) it may be concluded that they are basically 'rigid'.

To close it should be noted that these deductions above are general, drawn on a number of compounds, and it could be dangerous to consider single examples. For instance while subtraction of the 'rigid' line from the alkanes gives positive values for ΔS_c, in case of

butane, which is conformationally free, a negative number is obtained.

5. Conclusion

The manifest dependency of ΔS_f on ΔH_f enables some light to be shone on a number of aspects of the fusion process.

In particular it is evident that Walden's Rule has no general validity. It is interesting to note here that the ΔS_f data Walden collected has a very narrow range of only 5.2 J K^{-1} mol^{-1} (two standard deviations). 19 of his compounds can be found in Acree's set; his data from these show a virtually identical distribution. However the up-to-date values from Acree are almost three times more spread out.

There are certain implications for prediction of ΔS_f values. One recent scheme [24] has utilised a group additivity approach, which seems counter-intuitive, but presumably works because ΔS_f is dependent on ΔH_f so that it is really the latter that is being predicted. If the data set is kurtosed a false sense of precision may be generated because the numbers are clustered.

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