Accepted Manuscript

Estimation of melting points of organics

Samuel H. Yalkowsky, Doaa Alantary

Please cite this article as: Yalkowsky SH, Alantary D, Estimation of melting points of organics, *Journal of Pharmaceutical Sciences* (2018), doi: 10.1016/j.xphs.2017.12.013.

Estimation of melting points of organics

Samuel H. Yalkowsky[1], Doaa Alantary[1]
[1]College of Pharmacy, University of Arizona, Tucson, AZ 85721

ABSTRACT

UPPER (Unified Physical Property Estimation Relationships) is a system of empirical and theoretical relationships that relate twenty physicochemical properties of organic molecules to each other and to chemical structure. Melting point is a key parameter in the UPPER Scheme because it is a determinant of several other properties including vapor pressure, and Solubility. This review describes the first principals calculation of the melting points of organic compounds from structure. The calculation is based on the fact that the melting point, T_m, is equal to the ratio of the heat of melting, ΔH_m, to the entropy of melting, ΔS_m. The heat of melting is shown to be an additive-constitutive property. However, the entropy of melting is not entirely group additive. It is primarily dependent on molecular geometry, including parameters which reflect the degree of restriction of molecular motion in the crystal to that of the liquid. Symmetry, eccentricity, chirality, flexibility, and hydrogen bonding, each decrease molecular freedom in different ways and thus make different contributions to the total entropy of fusion. The relationships of these entropy determining parameters to chemical structure are used to develop a reasonably accurate means of predicting the melting points over 2000 compounds.

BACKGROUND

The melting point is by far the most commonly reported property of organic compounds. It is often among the first properties determined after a new compound is synthesized. There is probably more melting point data available for organic compounds than any other physical, chemical, or biological property. In spite of the tremendous amount of available melting point data, the calculation of the melting point form chemical structure remains an elusive problem. Although melting point is analogous to boiling point, it is far more difficult to predict. The reason for this difficulty is that the melting point of a compound is not solely dependent upon the pairwise interactions of the molecules at the phase transition temperature, as is its boiling point. The melting point is also dependent upon the far less predictable ability of the molecules to be properly arranged for maximum attractive interaction in the crystal lattice. According to Pauling[1,2,] the rate of a crystalline molecule leaving its lattice is dependent only upon its thermal energy, whereas the rate of incorporation into the lattice is dependent upon both thermal energy and alignment.

As a result of the greater complexity of melting compared to boiling, there have been far fewer attempts to estimate melting point form structure than there have been for boiling point. Many of these have been reviewed by Bondi [3,4], Horvath[5], Baum[6], Reinhard and Drefahl[7], Tesconi and Yalkowsky[8] and Katritzky [9,10]. In reviewing the various attempts to estimate melting points. Dearden [11,12] showed that most approaches are restricted to very small series of compounds. Furthermore, Dearden showed that some studies use different prediction schemes

for different classes of compounds in order to gain accuracy. The major exceptions are the group contribution scheme of Joback [13] and Joback and Reid[14] and the two-tier scheme of Constantinou and Gani [15]. More recently Jain and Yalkowsky[16] showed that the combination of separate enthalpy and entropy estimations gives very good estimates of the melting points of over 2000 compounds, including many drugs and drug-like molecules.

As discussed by Gavezzotti [17] crystal structure is not predictable with current technology. The complexity of the relationship between melting point and structure can be appreciated by contrasting it to the boiling point data. Much of the added complexity of the melting point data results from the fact that the entropy of melting is more complex than the entropy of boiling. This is logical if it is assumed that the probability of a molecule being properly aligned and conformed for incorporation into the crystal lattice is dependent upon its eccentricity, symmetry, chirality, and flexibility.

Carnelley[18,19] was the first to note the effect of molecular geometry on melting point. According to Brown and Brown [20,] Carnelley's rule states "of two or more isometric compounds, those whose atoms are the more symmetrically and the more compactly arranged melt higher than those in which the atomic arrangement is asymmetrical or in the form of long chains." Martin and Yalkowsky [21] were the first to interpret and quantitate the role of molecular symmetry and flexibility in determining the entropy of melting and thus the melting point. They observed that the melting points of a number of disubstituted benzene isomers are logarithmically related to their rotational symmetry number. They concluded that the effect of symmetry upon the melting point is due primarily to differences in their orientational or rotational entropies of melting. This is consistent with Pauling's [1,2] contention that "melting is related to intermolecular attraction, whereas recrystallization is related to both intermolecular attraction and orientation." This review describes the first principals calculation of the melting points of organic compounds from structure as illustrated by the UPPER model (Unified Physical Property Estimation Relationships).

ENTHALPIC FACTORS AFFECTING THE MELTING POINT

Melting is a complex process which is dependent upon the balance between the enthalpic forces holding the molecules in their crystal lattice and the effect of entropy which favors the break-up of the crystal lattice. The former is equal to the sum of all pairwise intermolecular attractions between the atoms and groups on one molecule with the atoms and groups on all of its neighbors. Consequently, the melting point is influenced by molecular geometry which determines how easily the molecules can become arranged to maximize the enthalpic interactions. The following sections provide a qualitative description of the energetic and geometric factors that determine the melting points of organic compounds

Group Contribution Values

Organic molecules can be divided into structural fragments (i.e., atoms or groups) according to a number of schemes. Although the fragmentation pattern used in UPPER is the AQUAFAC (Aqueous functional groupactivity coefficients) scheme developed by Myrdal et al. [22] and used

by Lian and Yalkowsky [23,24], Admire and Yalkowsky [25], and Alantary and Yalkowsky [26] other group contribution schemes can be used in the calculation of the enthalpy of melting.

Each atom or group on a molecule will contribute to the total enthalpy of melting depending on its size, dipole moment, and hydrogen bonding ability, as well as its environment. These group contribution values are determined by statistical analysis of the molecular fragments and experimentally measured enthalpies of melting. Since there are a variety of fragmentation schemes, values proposed for the same group by different authors often are not identical. However, the total enthalpies calculated for most molecules are usually similar. The only group additive property considered in UPPER is heat or enthalpy of fusion or melting $\triangle H_m$. The interaction energy between two groups is proportional to the product of their polarizabilities, or molar volumes, and the reciprocal of the sixth power of the distance between the interacting groups

Molecular polarizability is a direct measure of molecular volume. It can be calculated as the sum of group contributions or bond contributions. Their values for some groups and bonds are given in Table 1. Molecular polarizabilities calculated by both methods are usually in good agreement with one another.

Enthalpic Descriptors:

The UPPER approach of Yalkowsky et al.[24,25,26] is used to describe and quantitate the relationships among molecular properties. It treats certain properties as additive constitutive properties which reflect enthalpic interactions. All additive constitutive schemes for melting enthalpy have the general form

$$\Delta H_{molec} = \sum m_i n_i \qquad\qquad\qquad 2$$

where ΔH_{molec} is the heat of melting of the whole molecule, the m_i are the contributions of molecular fragment or group i to the total enthalpy of fusion and n_i is the number of fragment i in the molecule. The m_i values are calculated by multiple linear regression of fragment composition against the experimental molecular property values.

Each additive-constitutive molecular fragment in the UPPER scheme is defined as the smallest group of atoms (consisting of all carbons, hydrogens, and hetero atoms, including their non-bonded electrons) that are not separated by an isolating carbon. An isolating carbon was defined by Leo [27] as a carbon atom that is not doubly or triply bonded to a heteroatom.

Each fragment, i, is described by its chemical formula and by its environment. The chemical formula is written in the traditional manner with "=" and "≡" representing double and triple bonds, respectively. The environmental designation of a group refers to the hybrid state of its isolating carbon as illustrated in Table 2. The m_i values determined by Lian and Yalkowsky [23,24], Admire et al. [25], and Alantary and Yalkowsky [26] are summarized in Table 3.

The most obvious effect of structure on melting point is molecular size. All groups (including nonpolar, dipolar, hydrogen bonding, as well as aromatic and aliphatic) contribute to dispersion forces according to dipole moments and the size of their polarizable electron clouds. A series of alkanes with different carbon numbers is a homologous series. Any non-methylene

group on a hydrocarbon chain is referred to as a loading group. Loading groups can have a profound effect on the dependence of the measured property on carbon number for homologs.

Hydrocarbon Groups

The contribution of a hydrocarbon group to the van der Waals intermolecular interaction energy is reflected in its m_i value. Hydrocarbon groups are attracted to each other primarily by dispersion forces that are determined by their polarizabilities, which are, in turn, a measure of the size of their electron clouds.   Since the total intermolecular attraction between two molecules is the sum of the pairwise atomic or group interactions, increasing the number of atoms or groups on a molecule will increase its interactions with neighboring molecules.

The m_i value of a group is equal to its contribution to the total heat of fusion of the molecule. The m_i values of the most common hydrocarbon groups are listed in the top section of Table 3. Although certain C-H bonds have significant dipole moments (e.g., hydrogen cyanide, formaldehyde, chloroform). The dipole moments of most C-H bonds are of very low magnitudes and do not have a great effect on the melting point.

Dipolar Groups

Heteroatoms and heteroatom-containing groups have m_i values that are dependent upon their dipole moments as well as on their polarizabilities. Since dipoles interact with electron clouds as well as with other dipoles, they have greater m_i values than their hydrocarbon homomorphs. This is evident from the m_i values in the central portion of Table 3

Dipoles interact with other dipoles in the same way as magnets interact with one another. The arrangement of dipolar molecules is a balance between the closest packed arrangement driven by dispersion forces and the alignment of the molecular dipoles. If the dipoles are well aligned, dipolar forces are much stronger than dispersion forces. Many compounds have multiple dipoles. Depending on how they are arranged and on how flexible the molecule is, these dipoles can complement each other or compete with each other and with dispersion forces to determine the most stable crystal structure. If two or more of these arrangements are stable, the compound may exist in polymorphic forms.

Dipole-dipole forces, unlike dispersion forces, are directional, i.e., they favor a particular orientation of the molecules, with respect to one another. Since the most energetically favorable arrangement of molecules for dipolar interaction will very likely not be the same as the most densely packed arrangement favored by dispersion forces, the two forces must compete for control of the crystal lattice arrangement. For a hypothetical two dimensional crystal of carbon dioxide, the most favorable arrangement for dipolar interactions has the very open structure of Figure 1a, whereas dispersion forces favor the more densely packed arrangement of Figure 1b. The hypothetical extreme *a* and *b* arrangements are among the least favorable from a dispersion and dipolar perspective, respectively. A compromise arrangement such as in Figure 1c allows for favorable dipolar interactions without too great of a loss of dispersion interactions.

Dipolar groups invariably strengthen the crystal lattice over that of a homomorphic hydrocarbon and increase melting point. For simple compounds, the effect is usually quite consistent (See Table 3) Note that generally for both aromatic and aliphatic compounds, the order of m_i values is $CH_3 \leq F \leq Cl \leq Br \leq I$. This order is not strictly a dipole moment effect or the halogens would have nearly the same melting points. The differences among halogens are due to the differences in polarizability, which follow the differences in atomic size. However, if polarizability were the only important factor, then methyl compounds would melt between their chloro and bromo counterparts. Likewise, the nitro compounds with large polarizabilities and dipole moments melt higher than their corresponding halo or hydrocarbons.

Hydrogen Bonding Groups

A hydrogen bond is formed by a hydrogen atom that is covalently bonded to an electronegative atom (A) and is interacting with another electronegative atom (B) to which it is not covalently bonded. The hydrogen bond can be thought of as a three atoms sigma orbital in which the hydrogen is shared by both A and B. This is depicted as A–H···B, where A–H is the hydrogen donor and B is the acceptor. The most important property for determining the melting point of an unionized drug molecule is its ability to form an intermolecular hydrogen bonded network. In general, if a hydrogen bond is possible between molecules it will be formed in the crystal. However, as the molecules arrange themselves to form the hydrogen bond, they will likely assume a packing arrangement which is not as efficient as that of the non-hydrogen bonding homomorph. (The highly expanded structure of ice is an extreme example of the loss of packing efficiency that can result from hydrogen bond formation).

The bottom portion of Table 3 lists the m_i values of groups containing OH or NH bonds. These hydrogen bonding groups have the largest m_i values because hydrogen bonds are much stronger than dispersion and dipolar interactions. It is clear that the m_i values of the hydrogen bonding groups are significantly greater than those of the nonpolar and dipolar groups in the table.

Because of the strict geometric requirements, and the great interaction energy, of a hydrogen bond, the packing arrangements of hydrogen bonded crystals tend to be even less dense than that of crystals of dipolar molecules. Figure 2 shows a hypothetical two-dimensional packing arrangements of water with the arrangements dominated by a: hydrogen bonding, b: dipolar interactions, and c: dispersion forces.

Hydrogen Bond Strength

The strength of an A-H···B bond depends primarily upon the electronegativity of the A and B atoms, on the closeness of the A-H···B angle to 180°, and on the distance between the electronegative atoms A and B. The linear A-H···B distance is invariably less than the sum of the van der Waals radii of A and B and more than the sum of their covalent radii. This is illustrated schematically in Figure 3, which also illustrates the effect of A-B distances and A-H···B angle on the strength of a hydrogen bond. The difference in distance between (A-H and H...B) the bondable hydrogen and the acceptor atom is a measure of the strength of the hydrogen bond.

These differences are shown in Tables 4 and 5. The relative strengths of the most common hydrogen bonds are generally in the following order

$$F–H\cdots F > O–H\cdots N \sim O–H\cdots O > N–H\cdots O \sim N–H\cdots N > O–H\cdots F \gg O–H\cdots C$$

This order can be altered by the electronic effect of substituents that are bonded to the heteroatoms.

Reinforced Hydrogen Bonds

The effect of a second hydrogen bonding group on a molecule is far less consistent than that of the first. If a molecule contains groups that can form hydrogen bonds that are parallel and coplanar to each other, there will usually be an increase in the melting point. An additional hydrogen bond, which is parallel to an existing hydrogen bond, requires little or no additional constraints on the molecular arrangement. In fact, the chances of formation of the second hydrogen bond will likely be enhanced by the existence of the first hydrogen bond. Examples of reinforced hydrogen bonds in the crystal are found in water as well as in carboxylic acids, amides, and lactams that can form cyclic dimers with parallel hydrogen bonds as shown in Figure 4. These groups invariably melt higher than similar alcohols, amines, and lactones.

Maximum Hydrogen Bond Number

The maximum hydrogen bond number (MHBN) is defined as the number of molecules that can be hydrogen bonded to other molecules in a repeating lattice. It is equal to twice the minimum of the number of donor and acceptor groups on the molecule. As illustrated in Figure 4, water has two bondable hydrogens and two electron pairs, on each oxygen atom so that each water molecule can be involved in four hydrogen bonds (MHBN=4). Ammonia has three hydrogens but only one electron pair acceptor so that only two hydrogen bonds per molecule can exist in a repeating lattice (MHBN=2). Similarly, primary amine lattices can have only two hydrogen bonds per molecule. Hydrogen fluoride, ethanol, phenol, and secondary amines each have a single bondable hydrogen and can thus have only two hydrogen bonds per molecule in the crystal. Ethylene glycol, as well as dihydroxy and dicarboxy benzene isomers, could, like water, have four hydrogen bonds per molecule in a repeating lattice; provided that there are no geometric restrictions to both sets of bonds forming.

Unformed Hydrogen Bonds

The melting points of multiple hydrogen bonding compounds are invariably lower than would be expected from the MHBN. The geometric requirements of the second group are likely to be in conflict with those of the first hydrogen bond as well as with van der Waals attractions. Consequently, the effect of a third hydrogen bonding group on melting point is generally much smaller than that of the second group and may be insignificant. (Hydrogen bond groups that reinforce the existing groups are obvious exceptions.) Furthermore, the geometry of the molecule can cause the additional hydrogen bonds to be excessively non-linear or elongated, or prevent their formation altogether.

In general, all possible hydrogen bonds often cannot be formed because all of the donor and acceptor groups cannot be properly aligned for bonding in a repeating lattice. The geometric constraints imposed by the first two bonds will usually prevent hydrogen bonding groups from being at the proper position for interaction with existing groups. In fact, it would be impossible to construct a repeating lattice of the tetra-, penta- or hexa-carboxyl benzene in which each carboxyl group is involved in two hydrogen bonds. Such an arrangement would require that each molecule donate four or more hydrogens to an intermolecular hydrogen bond, and thus be involved in at least eight hydrogen bonds. Similarly, compounds such as glycerin, gallic acid and sugars melt lower than expected from their number of possible hydrogen bond donating and accepting groups.

Intramolecular Hydrogen Bonding

Intramolecular hydrogen bonding is the interaction of A-H group with a B group on the same molecule. Optimum intramolecular hydrogen bonding most often occurs when the hydrogen closes a flat six-membered ring that is stabilized by a double bond. The double bond increases the likelihood of the donor and acceptor groups being coplanar while placing no restriction on the free rotation of the hydrogens. Dearden[29] and Katritzky et al[9] noted that if intramolecular hydrogen bonding occurs, the groups involved will be less available for intermolecular bonding.

Intramolecular hydrogen bond formation of compounds that contain a single donor hydrogen (from OH, NH, COOH, or CONH) that forms a six-membered ring which is stabilized (held planar) by a double bond can significantly decrease the intermolecular enthalpic effect of a hydrogen bond. Compounds such as ortho-nitrophenol, ortho-methoxy benzoic acid, etc., which can form six-membered rings by intramolecular hydrogen bonding have lower melting points than their meta and para isomers. The higher melting points of the para isomers is a result of their greater symmetry as well as the fact that they do not form intramolecular hydrogen bonds.

Overall Effect of Hydrogen Bonding

In general, if a molecule has a hydrogen bonding group, it will be the dominant factor in determining its crystal structure and stability. Therefore the addition of the first hydrogen bonding group will invariably produce a significant increase in the melting enthalpy. However, the single hydrogen bond will compete with dipolar and dispersion interactions in determining the most stable crystal structure. The effect of the addition of a second hydrogen bonding group is less certain. Depending upon where it is located on the molecule, a second hydrogen bonding group will likely produce a smaller increase in melting point than does the first group. It will also compete with other hydrogen bonding groups to determine the crystal lattice. Fortunately, intramolecular hydrogen bonding is only prominent in specific cases which are easily identified. (Note also that intramolecular hydrogen bonding is not a dominant effect for dissolved compounds because water, which is present in very large excess, can bond to both hydrogen donor groups and acceptor groups.

Homologs

Figures 5-9 show the effect of multiple additions of simple methylene groups to the heat of fusion for several parent molecules. The figures tend to be consistent with one another in most, but not all, cases. The best examples of the contribution of a group to the heat of fusion are the alkyl homologs. Figures 5 through 9 show a linear dependence of the heat of fusion on the

number of methylene carbons in the normal alkanes, alkenes, and alkylbenzenes, respectively. In each case, the slope is close to the m_i value for a methylene group.

Odd-Even Alteration

The melting points of the members of many homologous series that contain an odd number of carbons are often described by a slightly different curve than are the even carbon compounds. This odd-even alteration of the melting point is most pronounced for compounds with low carbon numbers. The even carbon and odd carbon curves tend to merge as the carbon number increases. These differences arise from subtle differences in packing arrangement and therefore are not seen in the boiling point data.

Odd-even alteration in melting point at first seems rather strange and unexpected. It is tempting to expect that adding a CH_2 group to an even carbon alkane would be the same as adding it to an odd carbon alkane. In the normal alkanes, the addition of successive methylene groups changes the angle between the terminal carbon-carbon bonds from $180°$ for n even to $109°$ for n odd. The UPPER scheme does not account for differences between odd and even carbon homologs.

Loading Groups

A homologous series can be produced by the addition of a polymethylene group to a loading group (where a loading group is any nonpoly-methylene group). In general the heats of fusion of homologous series increase with increasing carbon number and converge towards the value of paraffin. However, the effect of the first few methylene groups is less consistent. For example, if the loading group contains an OH, COOH or NH moiety, the effect of alkylation of the carbon will be as described for alkanes and dipolar groups. However, if alkylation changes the loading group to produce an ether, ester or primary amine that is less capable of hydrogen bonding with neighboring molecules, the resulting less polar molecule may have a much lower heat of fusion than the original molecule. In either case, as additional methylene groups are added the heat of fusion will begin to increase with carbon number.

The above is also true for homologation of dipolar and aromatic compounds. The first methylene group can reduce the enthalpy of melting by interfering with packing, or it can simply increase the enthalpy of melting. Progressive increases in carbon number will produce a monotonic increase in the heat of fusion. Thus for any loading group there may or may not be a decrease in the enthalpy of fusion. However, there will invariably be an increase in the enthalpy of fusion as alkyl chain length is increased.

Figures 5 thru 9 show the heats of fusion of the members of some homologous series. It can be seen that the hydrogen bonding homologs tend to have higher enthalpies than the dipolar homologs and the hydrocarbons have the lowest enthalpies of melting. The Figures also show that the differences among the series are large for the short chain compounds and that the curves merge as alkyl chain length increases and the properties of the homologs become progressively more similar to those of paraffin.

Polymethylbenzenes

The effect of adding methylene groups directly to a benzene ring is shown in Figure 8 (For purposes of illustration the isomers are presented on the x-axis in the order of their symmetry). On the basis of the average of the dimethyl-, trimethyl, and tetramethyl isomers, there is a clear increase in the heat of fusion with increasing carbon number.

It is clear from Figure 9 that adding a ring methylene group to a cycloalkane generally increases the heat of fusion for small rings. However, because larger rings have stricter angle requirements, the data become erratic for cyclic compounds containing more than ten carbons.

Polycyclic Aromatic Hydrocarbons.

Figure 10 shows that relation between the heats of fusion of polycyclic aromatic hydrocarbons (PAH) and the total number of carbons in the molecule. Comparison with Figure 5 indicates that the enthalpy of melting is far less sensitive to the number of aromatic carbons than the aliphatic carbons. The figure also shows that there is significant scatter from the regression line for the aromatics. This is due to the fact that, unlike homologs, which consist primarily of methylene groups, the PAHs are composed of several groups, CHar, Car, Cbip, CBR1, and CBR2. In addition, the PAH molecules have different shapes, symmetries, chiralities, and packing efficiencies, and can associate by interaction of their planar regions.

ENTROPIC FACTORS AFFECTING THE MELTING POINT

Calculation of the total heat of fusion

As stated above, the addition of any group to a molecule will increase its heat of fusion by its m_i value, according to equation 2.

In order to understand why melting is much more difficult to predict than boiling, and why some isomers have different melting points. Besides the reasons for the differences in the melting points of isomers, it is necessary to appreciate the role of entropy in the melting process. Every molecule of a crystal is confined in several ways within its lattice. It is restricted in its conformation, as well as in its distance from and orientation with respect to its nearest neighbors. Upon melting, these restrictions become greatly relaxed so that molecules can exist in a greater number of positions, orientations, arrangements, and conformations in the liquid.

Since all of the enthalpic intermolecular interactions described above contribute to an ordered molecular arrangement, they must be opposed by entropy, which favors disorder. The entropy of fusion has been proposed to be group additive and constitutive by Chickos et al[31, 32], and Coutsikos et al[33]. However, the different melting points of isomers prove that entropy cannot be solely group additive. Nevertheless, there are certain regularities between melting entropy and chemical structure that can form the basis for a better practical and theoretical understanding of melting. The five entropy descriptors used in UPPER: (translation, symmetry, eccentricity, chirality, and flexibility) are based on geometric differences between the liquid and the solid. As described below, some of them are additive and constitutive, and some are not.

The entropy of one mole of a substance being in a crystal, $\triangle S^C$ is related to the number of ways Ω^C that it can be arranged (i.e., number of microstates) that conform to the geometric requirements of the crystal and the liquid by

$$\Delta S^C = R \cdot \ln \Omega^C \quad \text{and} \quad \Delta S^L = R \cdot \ln \Omega^L \qquad\qquad 3$$

The entropy of a phase transition is defined as the entropy of the final state minus the entropy of the initial state. Therefore, the entropy of melting, $\triangle S_m$ is

$$\Delta S_m = R \cdot \ln \left| \frac{\Omega^C}{\Omega^L + \Omega^C} \right| \qquad\qquad 4$$

Translation, W

Based on the fact that the ratio of the volume of an organic compound as a gas to its volume as a liquid is reasonably constant, Trouton's[34] rule states that the entropy of boiling of most organic compounds is constant at about 84 J/Kmol. By analogy to Trouton's rule, Walden's[35] rule states that the entropy of melting for organic compounds can be described by

$$\Delta S_m = W \qquad\qquad 5$$

where *W* is a constant. In the case of coal tar derivatives (i.e., aromatic compounds) the value of *W* for melting is close to 57 J/Kmol. Since the entropy of boiling describes the complete separation of molecules, it is greater than the entropy of melting, which relates to only partial separation of the molecules. Thus Walden's constant is much smaller than Trouton's constant.

Symmetry, σ

Although Carnelley was the first to recognize that symmetrical molecules tend to melt higher than their less symmetrical isomers, Martin et al[21] and Yalkowsky[36] were the first to interpret and quantitate the role of molecular symmetry in determining the entropy of melting and thus the melting point. They observed that the melting points of a number of disubstituted benzene isomers are logarithmically related to their rotational symmetry number. Because the enthalpies of melting of isomers are similar, they concluded that the effect of symmetry on the melting point is primarily due to differences in their rotational, entropies of melting.

As discussed by Dannenfelser et al[37] the molecular external rotational symmetry number, σ, is the rotational degeneracy of the molecule. It is the number of positions into which it can be rotated that is identical to a reference position. The symmetry numbers of some representative compounds are illustrated in Figure 11. Symmetry reflects the probability of a molecule being properly oriented for incorporation into the crystal lattice, and its logarithm reflects the orientational entropy of melting. Because of the effect of symmetry on the entropy of melting, symmetrical molecules are more easily crystallized and have higher melting points than less symmetrical molecules of the same size. A molecule with a high symmetry number, e.g., benzene ($\sigma = 12$) has a much greater number of orientations available to it for crystallization than an asymmetric molecule, e.g. 3-chlorotoluene ($\sigma = 1$), toluene ($\sigma = 2$), or even p-xylene ($\sigma = 4$). The greater orientational freedom associated with high values of σ tends to favor the formation of a crystal. In other words, increasing symmetry tends to increase melting point of compounds. This is illustrated by the data for several groups of isomers and near isomers in Figure 12. In each case the highest melting point corresponds to the most symmetrical structure, in accordance

with Carnelley's rule. Dannenfelser et al.[37] showed that the contribution of symmetry to the total entropy of fusion is given by

$$\Delta S_m{}^{rot} = S_m \log \sigma \qquad\qquad 5$$

where S_m is a regression derived constant.

Eccentricity, ε

Another important non-additive non-constitutive descriptor of a molecule is its overall shape. This is a primary determinant of its ability to pack efficiently in the crystal. Unfortunately, it is generally not possible to predict the packing arrangement of organic molecules. It is also not possible to define a simple shape descriptor that accurately accounts for the effects of molecular shape on intermolecular interactions in the crystal or for the expansion that will occur upon melting of that crystal. Johnson and Yalkowsky[38] showed that including a dimension based molecular shape descriptor and a chirality descriptor along with the symmetry and flexibility descriptors greatly enhance the calculation of the entropy of melting and thus the melting point of hydrocarbons. They used the eccentricity number, ε (defined as the sum of the number of atoms that are in or on aromatic rings.) as a measure of the "flatness" of a molecule. Since flat molecules pack efficiently, they tend to need more room for the expansion that accompanies melting. Thus, they require more energy and a higher temperature to melt.

Chirality, χ

The chirality number, χ, indicates the number of 3 dimensional molecular species present in the sample, i.e., whether it is a pure substance or a mixture of optical isomers. A simple racemic mixture has a chirality number of 2 because it consists of two entities. The isomers will be randomly distributed in the liquid, but they must either form pairs to crystallize as a single molecular compound or they must separate to crystallize as two pure isomers. In either case, the crystal(s) are more ordered than the liquid and the entropy of fusion is larger than that of a pure single compound. Leclercq et al[39] evaluated the crystallization of over 50 chiral compounds and showed that the enthalpies of fusion and melting points of racemates tend to be lower than those of their pure D and L isomers

Some molecules that do not have an asymmetric carbon can be optically active. For example, Figure 13 illustrates that 1,2,9,10-dibenzphenanthrene (pentahelicene) cannot be completely planar because that would require two atoms to occupy the same space. These molecules must exist in a spiral arrangement. Since left and right handed spirals are mirror images, they can crystallize either as mirror-pairs or as separate right and left spirals. This may also be the case for 1,2-benzphenanthrene (tetrahelicene) but not for 1,2-benzanthracene which is not chiral.

Johnson and Yalkowsky[38] showed that the melting points of polycyclic aromatic hydrocarbons (such as (+) pentahelicene) which are forced into left or right spiral conformations are racemates and have lower melting points than would be expected on the basis of the values their 2D structures. Chirality number is equal to unity for achiral substances and optically pure chiral compounds such as (+,-) pentahelicene or DL-glycine as well as most organic compounds.

It can be larger for diastereomers if all four forms are present. Recently Hartley[40] showed that ortho-oligophenylenes exist primarily as enantiomeric spirals.

Johnson and Yalkowsky[38] also showed that the contributions of eccentricity and chirality to the total entropy of fusion are given by

$$\Delta S_m{}^{exp} = E_m \log \varepsilon \qquad\qquad 6$$

and

$$\Delta S_m{}^{chiral} = X_m \log \chi \qquad\qquad 7$$

respectively

Flexibility

Organic molecules that are composed either partially or entirely of single bonds in chains are considered flexible. The most common flexible organic moiety is the polymethylene chain. In the crystal, these molecules or their flexible segments tend to be aligned in a parallel linear fashion, which enables maximum dispersion interaction between chains. These alignments are highly restrictive and require the trans conformation of all bonds.

The likelihood of a series of connected methylene groups being trans is the key determinant of the effect of chain length on the entropy of fusion and thus the melting point. The basic torsional conformation unit is a linear four atom chain, as depicted by the Newman projection of butane in Figure 14. If a four carbon unit such as butane has only three equally stable conformations, placing the terminal methyl groups at torsional angles of 60, 180, and 300, the probability of a butane molecule being in the trans conformation would be 0.333.

The number of torsional units, Φ, in an aliphatic chain is equal to the number of different four-atom segments that can be selected from the molecule. For example, hexane has three (3) torsional units: C1-C4, C2-C5, and C3-C6. Thus, the probability of hexane being all trans would be $(0.333)^\Phi$. The value of Φ is equal to n-3 where n is the number of sp^3 atoms in the chain. SA pair of double bonded sp2 atoms has less rotational freedom and is counted as a single unit. Atoms in one or more rigid ring systems as well as linear sp atoms do not contribute to flexibility and are therefore not counted. Although they were not aware of Carnelley's work at the time, Tsakanikas et al[41] and Dannenfelser et al[37,42] quantitated his observations by showing that the melting point and entropy of melting, for over 1000 compounds are highly correlated with the logarithms of both the molecular symmetry number and the molecular flexibility number. They defined the molecular flexibility number, ϕ, as

$$\phi = F^\Phi \qquad\qquad 8$$

where F is the probability of a single torsional unit (a linear chain of four atoms) being trans (180°) and Φ is the number of torsional units in the molecule. The contribution of flexibility to the total entropy of melting is

$$\Delta S_m{}^{conf} = C_m \log \phi = C_m \Phi \qquad\qquad 9$$

where C_m is a regression derived constant that incorporates the value of logF.

Wunderlich[43] has shown that the trans conformation is more stable than the gauche confirmations and that certain combinations of torsional angles are forbidden because they would place two atoms in the same place at the same time. Based on experimental data the probability of each torsional unit being in the trans conformation is close to 0.400. Applying equation 8 gives the entropy of fusion per methylene group at about 7.4 J/K.mol of CH_2 groups. However, it will decrease slightly as chain length increase, and thus the number of forbidden conformations increase.

Hydrogen Bonding

Alantary and Yalkowsky [26] showed that hydrogen bonding has a significant effect on the total enthalpies melting and boiling, and on the entropy of boiling, but only a slight effect on the entropy of melting Because melting does not totally separate molecules from their neighbors hydrogen bonds exist in the liquid as well as in the solid. Although the hydrogen bonding pattern of the liquid is less ordered than in the crystal the effect of the entropic difference is overshadowed by the enthalpic difference. Therefore hydrogen bonding is not used in the calculation of the entropy of fusion.

Calculation of the Total entropy of fusion

Since some of the entropy determining parameters described above are not group additive, it is obvious that no simple group contribution scheme will be able to adequately predict melting point; even for fairly simple molecules. Fortunately, the following generalization has been found to be useful.

$$\Delta S_m = W_m - S_{m.} \log \sigma + E_{m.} \log \varepsilon + X_m \cdot \log \chi + C_m \cdot \log \phi \qquad 10$$

where A is a modified Walden's[35] rule constant and $\sigma, \varepsilon, \chi$, and ϕ are the non-additive, non-constitutive descriptors for symmetry, eccentricity, chirality, and flexibility, respectively. The data of Lian, and Yalkowsky [23,24], Admire et al. [25], and Alantary and Yalkowsky [26] for almost 3000 organic compounds indicate that provides a reasonable approximation of the observed values.

$$\Delta S_m = 45.0 - 8.9 \cdot \log \sigma - 2.2 \cdot \log \sigma' + 11.4 \cdot \log \varepsilon + 5.9 \cdot \phi \qquad 11$$

For most organic compounds, the symmetry, eccentricity, and chirality terms are small, and the entropy of fusion is primarily determined by a constant and molecular flexibility. For non-flexible molecules (including nearly all small aromatic compounds) Walden's rule is a good approximation of the true entropy of fusion. Note that for many coal tar derivatives the value of 57 kJ/mol is close to 50kJ/mol plus an eccentricity term. Note also that for globular and highly symmetrical molecules the addition of the negative symmetry term reduces the entropy of fusion to conform to Richard's[44] rule constant of 15 kJ/mol.

On the other hand, the flexibility term for alkyl homologs indicates a constant, and large, increase in the entropy of fusion with increasing flexibility. The most commonly encountered flexible moiety is the simple polymethylene chain. Long aliphatic chains occur naturally in most fats and oils and are often added to existing molecules to alter solubility or partitioning properties. The flexibility of alkyl homologs (and thus the total entropy of melting) is proportional to the number of carbons in the chain. This can be seen from the data in Figures 5-7. These Figures show that adding a carbon containing group raises both the enthalpy of melting and the entropy of melting. Since the increase in enthalpy is greater than the increase in entropy, the melting points of homologs invariably increase with increasing carbon number

13

CALCULATION OF THE MELTING POINT

Thermodynamically, the normal melting point is the temperature at which the solid and liquid are at equilibrium at one atmosphere pressure. Since the free energy of a system at equilibrium is equal to zero, the Kelvin melting point, T_m is equal to

$$T_m = \frac{\Delta H_m}{\Delta S_m} \qquad \text{12}$$

where ΔH_m is the total heat (or enthalpy) of melting and ΔS_m is the total entropy of melting.

According to equation 12, factors that either increase ΔH_m or decrease ΔS_m will contribute towards an increase in melting point. The major thrust of this section will be to separately consider the effects of structure on both the enthalpic and entropic factors that influence melting. The enthalpy of melting is generally accepted to be an additive constitutive property of chemical composition by

$$\Delta H_m = \sum n_i m_i \qquad \text{13}$$

where the m_i values are given in Table 1. Incorporating equation 10 and 12 into equation 9 gives

$$T_m = \frac{\sum n_i m_i}{45.0 - 8.9 \cdot \log\sigma - 2.2 \cdot \log\sigma' + 11.4 \cdot \log\varepsilon + 5.91 \cdot \Phi} \qquad \text{14}$$

Alkanes

Based on the above discussion, the enthalpy of fusion of alkyl homologs can be written as

$$\Delta H_m = A + B \cdot n \qquad \text{15}$$

where A is a constant that is dependent on the non-methylene portion of the molecule, i.e., the sum of their m_i values of the non flexible components of the molecule, and B is the m_i value of a chain methylene group (i.e., the slope of the enthalpy vs. n, curve of Figure 5). Likewise the entropy of melting of a series of alkyl homologs is

$$\Delta S_m = C + D \cdot n \qquad \text{16}$$

where C is the intercept of the ΔH_m *vs. n* line. It is primarily equal to the sum of the non additive components of the total entropy of melting. And D is the increase in the entropy of melting per methylene group (i.e., the slope of the entropy curve in Figure 5). Thus, homologation would be expected to produce a linear increase in both the enthalpy of melting and the entropy of melting.

Convergence Temperature

Incorporating these results into **equation** 12 gives the Kelvin melting point of a homolog of chain length n, as

$$T_m(n) = \frac{A + B\,n}{C + D\,n} \qquad \text{17}$$

where *A* and *C* are the contributions of the terminal group (i.e., the portion of the molecule that is not a linear alkane) to the enthalpy and entropy of melting, respectively, B is the contribution of

the methylene group to the enthalpy of melting (2.95 kJ/mol) and D is the contribution of the methylene group to the entropy of melting (7.4 J/K mol). Extrapolating to n = ∞, the above equation becomes,

$$T_m(n) \Rightarrow B/D = 399 \text{ K} = 126°C \qquad\qquad 18$$

This is quite close to the commonly reported value of 410K (or 137°C). (Because of deviations from linearity of both the enthalpy of melting and the entropy of melting, the convergence temperature calculated based on short chains (n < 20) are generally somewhat different than the experimental value obtained from the melting points of very long chain compounds.)

In the case of homologs the terms $\log\sigma$, $\log\varepsilon$, $\log\chi$ and their coefficients are small. However, the flexibility increases exponentially with increasing carbon number. This is illustrated in Figure 5. The linear increase in the enthalpy of fusion and the linear increase in the entropy of fusion produce a concave curve for the melting point as in Figure 5. Chickos and Nichols[45] showed that the experimental melting points ranging from 1 thru 400 converge to a constant value, which corresponds to the melting point of paraffin (410K).

The above relationship is similar to the equation of Broadhearst [46] which relates the melting point of a homolog to the convergence temperature and alkyl chain length by

$$T_m(n) = T_m(\infty)\frac{a+n}{b+n} \qquad\qquad 19$$

where a and b are equal to A/B and C/D from equations 14 and 15, respectively. Since $\frac{1}{n}$ approaches zero as n approaches infinity, extrapolating the reciprocal of n to zero is equivalent to extrapolating n to infinity. Therefore, a plot of the melting point, $T_m(n)$, vs. $\frac{1}{n}$ for any homologous series will intersect the y-axis at the convergence temperature. The convergence melting temperature indicates that the melting point curves for all homologous series approach the same value for very large values of *n*. This is essentially the melting point of paraffin, which is composed almost entirely of methylene groups. The convergence temperature is the ratio of the contributions of the enthalpy of melting of a methylene group to its entropy of melting. A convenient means of determining the convergence temperature is to plot the melting point (or the reciprocal melting point) vs. the reciprocal chain length. For small values of 1/n this usually gives a straight line that intercepts the y-axis at either the convergence temperature or the reciprocal convergence temperature. Figures 15 and 16 estimate the convergence temperature as 400K and 1/0.0024K, respectively, which are in reasonable agreement with each other and with the reported value of 410K.

Linear, Branched, and Cyclic compounds.

The effect of ring formation on the melting point is straightforward. The melting points of a selection of linear and cyclic analogs are shown in Table 6. In each case, the two terminal methyl groups of the linear compound are replaced by a single ethylene group to close the ring. The heats of melting of all of compounds can be calculated from the sum of the component m_i values. Although the m_i values of linear and cyclic groups are not identical, they generally do not differ greatly, so that we can assume that the enthalpies of melting for the linear and cyclic compounds are similar. Since the differences between the heats of melting for the pairs of

compounds in Table 6 are assumed to be small, the differences in the melting points must be largely dependent on the entropy of melting.

In the previous section, it was shown that flexibility is a significant determinate of the entropy of melting. Table 6 shows that the cyclic alkanes listed melt lower than their linear and branched near isomers. It is also the case for the heteroatomic compounds in Table 6. All of the non-hydrocarbon groups are the same for both compounds. Since the cyclic compounds are rigid, they have lower entropies of fusion and thus higher melting points, than their linear, more flexible counterparts.

The effect of branching on melting point is more complex. Branching, like cyclization, reduces the flexibility of linear compounds. This in turn reduces the entropy of fusion and increases the melting points of branched compounds. On the other hand, branched atoms are bonded to more than two atoms and are less able to interact with atoms on neighboring molecules. This causes them to have lower mi values and lower contributions to the heat of melting, then linear or terminal groups. Also, branching can increase symmetry (as in tert-butanol or neopentane) or decrease symmetry (as in 2-methylhexane and isopropyl alcohol).

Alkyl benzenes

The alkylbenzenes and alkylnaphthalenes provide an excellent example of the interplay of enthalpy and entropy in non hydrogen bonding systems. Figure 17 shows the melting points of strictly aromatic benzene (6°C) and naphthalene (80°C) as well as of their alkyl homologs. The melting points of the normal alkanes are included for reference. In both cases, the addition of the first carbon decreases the melting point by an average of near 100°C. This indicates that the reduction in symmetry and packing efficiency overrides the increase in fusion enthalpy in determining the melting point. For both aromatics, the melting points remain low as small numbers of carbons are added. This is likely due to their interference with both symmetry and lattice fit, which retards crystallization.

The melting points of the lower benzene homologs remain low as lattice fit is reduced and begin to increase with the 4th carbon, while those of the larger more crystalline naphthalenes remain low and do not begin to increase until the 6th or 7th carbon is added. Further addition of carbons produces an increase in melting enthalpy which is greater than the increase in entropy, and the melting points increase in a manner that parallels that of the simple alkanes.

This kind of relationship is common for the homologation of many biologically active compounds. It was first reported and explained by Flynn et al. [47] and Yalkowsky et al. [48] for the alkyl-p-aminobenzoates. The melting points decrease linearly for the first four homologs and then increase with the addition of carbons. They also showed that the effect of alkyl chain length on melting point parallels its effect on organic solvent solubility as well as aqueous solubility and membrane transport.

Dipolar and hydrogen bonding homologs.

The melting points of several alkyl homologs containing up to 18 carbons are given in Figure 18. It is clear that melting point of homologs increases with molecular weight and substituent

polarity. While these increases are primarily the result of increasing enthalpy, the irregularity of the increase of various series suggests that other factors are also important. For the simple alkanes (shown by the bold line) the overall shape of the melting temperature vs. carbon number plots are curved and level off as they approach the convergence temperature.

Single carbon compounds are rigid and usually have high symmetry (e.g., the methyl halides have the symmetry of a cone.) This gives them a lower entropy of fusion and higher packing efficiency than their two and three carbons congeners. Even when the single methylene addition lowers the melting point (as in the benzene and naphthalene derivatives), additional methylene groups do not produce a significant increase in the melting point until a critical carbon number is reached. See Figure 17. In all cases, however, increasing carbon number causes the melting point to approach the convergence temperature.

Polysubstituted benzenes

The polysubstituted benzenes listed in Tables 7 and 8 can be used to illustrate some of the applications of the UPPER approach as well as some of the complexities involved with predicting the melting points of complex compounds. In general, the melting points increase with increasing polar group substitution and thus increasing melting enthalpy. Not surprisingly, hydrogen bonding compounds have the highest melting points, and hydrocarbons have the lowest.

The first group added to a benzene ring increases enthalpy and decreases symmetry and packing efficiency. For many simple groups, the latter effects are dominant, and the melting points are reduced. As a result, most of the monosubstituted benzenes in Table 7 have melting points that are lower than that of benzene. Adding a hydrogen bonding group, on the other hand, produces a much greater increase in the melting enthalpy and may also enhance intermolecular bonding. As a result, most of the mono hydrogen bonded benzenes in Table 8 melt higher than does benzene. Also, as illustrated by the halogens, which are rigid substituents with similar dipole moments, melting points increase with increasing melting enthalpy due to increasing molecular size. However, increasing substituent size by homologation increases both the enthalpy and the entropy of fusion.

In the case of the hydrogen bonding compounds, the melting points tend to increase with substitution with groups that form reinforced hydrogen bonds having the largest effect. After that, the melting points become more random with respect to substituent number. This is because it is not usually possible to create a repeating lattice with complete multiple hydrogen bond formation. Furthermore increasing the number of hydrogen bonding groups on a molecule increases the likelihood of the formation of intramolecular hydrogen bonds.

The polysubstituted benzenes in Table 7 also show the effect of symmetry on the melting point. In most of the isomeric disubstituted, trisubstituted and tetrasubstituted derivatives, the most symmetrical compound has the highest melting point. This is illustrated in Figure 17

Disubstituted naphthalenes

Gavizzotti studied the melting points of a number of disubstituted naphthalenes and suggested that there is no proper theory of melting that can reliably predict melting point. However, the rotational symmetry number can reasonably distinguish between the melting points of isomers, just as it does for the substituted benzene isomers. Figure 19 shows Gavezzotti's experimental data for several sets of disubstituted naphthalenes as a function of position. The vertical dashed line is added to separate the compounds with σ = 1 from those with σ = 2. For each curve, the average melting point of the more symmetrical compounds is greater than that of the asymmetric group. This supports our contention that rotational symmetry is at least a partial determinant of melting point.

Summary and Conclusion

The UPPER approach to the calculation of the melting point of organic compounds is based upon the well known fact that the Kelvin melting point T_m is related to the enthalpy of melting ΔH_m and the entropy of melting ΔS_m by

$$Tm = \frac{\Delta Hm}{\Delta Sm}$$

The enthalpy of melting is easily calculated by simple group contribution approaches with good accuracy. On the other hand, the entropy of melting cannot be adequately calculated such an approach because it is dependent upon the whole molecule rather than upon the properties of individual molecular component groups. UPPER utilizes a constant, which is a modification of Trouton's law, along with four holistic, entropy determining properties i.e., symmetry, flexibility, chirality, and eccentricity, These properties are simple, intuitive and easily determined, from molecular constitution or by inspection, to
calculate the entropy of fusion

While the coefficients of the group contribution coefficients to the enthalpy of fusion and of the holistic properties to the entropy of fusion are determined by regression. No fitting is used to predict the melting temperature.

Figure 20 is a plot of the observed vs. predicted melting points determined by the above approach. The more than 2000 data points used are reported by lian and yalkowsky[24], Admire et al.[25], and Alantary and Yalkowsky[26]. The melting point data ranges from 85K to 698K and have an average absolute error of prediction of 38.6 K and a R^2 of 0.81.

REFERENCES

1. Pauling L. The structure and entropy of ice and other crystals with some randomness of atomic arrangement. J. Am. Chem. Soc 1935(57): 2680-2684.

2. Pauling L. General Chemistry. Dover Press, New York 1970,p 398.

3. Bondi A. A correlation of the entropy of fusion of molecular crystals with molecular structure. Chem. Rev 1967(67):565-580.

4. Bondi A. Physical properties of molecular crystals, liquids, and glasses. Wiley, New York 1968.

5. Horvath A. Molecular design, Chemical structure generation form the properties of pure organic compounds. Elsevier, Amsterdam 1992.

6. Baum E. Chemical Property Estimation: Theory and Application. Lewis, Boca Raton 1998.

7. Reinhard M, Drefahl AQ. Handbook for estimating physicochemical properties of organic compounds. Wiley, New York 1999.

8. Tesconi M, Yalkowsky S. Melting Point, in "Property Estimation Methods for Chemicals: Environmental and Health Sciences." Eds. D. Mackay and R.S. Bloething, CRC press, 1999, 3-27.

9.Katritzky A, Jain R, Lomaka A, Karelson M. Perspective on the relationship between melting points and chemical structure. Cryst. GFrowth Design 2001, 1(4): 261-265.

10.Katritzky A, Kuanar M, Slavov S , Hall CD, Karelson M, Kahn I, Dobchev D. Quantitative Correlation of Physical and Chemical Properties with Chemical Structure: Utility for Prediction. Chem. Rev. 2010, 110: 5714-5789

11. Dearden J, Ghafourian T. Hydrogen bonding parameter for QSAR of indicator variables. J. Chem. Inf. Comput. Sci.1999, 39(20); 231-235

12. Dearden J. Quantitative structure-property relationships for prediction of boiling point, vapor pressure, and melting point. Environ. Tox. & Chem. 2003, 22: 1696-1709.

13. Joback KG. A unified approach to physical property estimation using multivariate statistical techniques. MS thesis Mass Inst. Tech, Cambridge, MA 1982.

14. Joback K, Reid R. Estimation of pure component properties from group contributions. Chem. Engin. Commun. 1987: 233-243.

15. Constnatinou L, Gani R. New group contribution method. AIChE Journal 1994, 40(10): 1697-1710.

16. Jain A, Yalkowsky S. Comparison of two methods for estimation of melting points of organic compounds. Ind. Eng. Chem., Res.2007, 46: 2589-2592

17. Gavezzotti. Are crystal structures predictable?. Acc. Chem. Res.1994, 27: 309-314

18. Carnelley T. Chemical symmetry, or the influence of atomic arrangement on the physical properties of compounds, I Influence of atomic arrangement on melting point. Phil. Mag.1882, Series 5:112-130.

19.Carnelley T. Chemical symmetry, or the influence of atomic arrangement on the physical properties of compounds, II Influence of atomic arrangement on solubility. Phil. Mag. 1882, Series 5:180-193.

20. Brown R.F.C, Brown, R.F.C. Melting point and molecular symmetry. J. Chem. Ed. 2000, 77: 724-731.

21. Martin E, Yalkowsky S, Wells J. Fusion of Disubstituted Benzenes. J. Pharm. Sci., 1979, 68: 565-568.

22. Myrdal P, Ward G, Dannenfelser R, Mishra D, Yalkowsky S. AQUAFAC 1: Aqueous Functional Group Activity Coefficients: Application to Hydrocarbons. Chemosphere 1992, 24: 1047-1061 .

23. Lian B, and Yalkowsky S. A simplified approach to predict the heat of melting for organic compounds. Chemometr Intell Lab. 2011, 108(2):150-3.

24. Lian B, Yalkowsky S. Unified physicochemical property estimation relationships (UPPER). J.pharm.sci. 2014, 103 (9): 2710-2723

25. Admire B, Lian B, Yalkowsky S. Estimating the physicochemical properties of polyhalogenated aromatic and aliphatic compounds using UPPER, Boiling point and melting point. Chemosphere 2015, 119: 1436-1440

26. Alantary D, Yalkowsky S. Estimating the physicochemical properties of poly-substituted aromatic compounds using UPPER. J Pharm Sci 2018. DOI: http://dx.doi.org/10.1016/j.xphs.2017.10.018

27. Leo AJ. Calculating Log P (Oct) from Structures. Chem Rev. 1993, (4):1281-306.

28. Dearden J. The qsar prediction of melting-point, a property of environmental relevance. Sci. Tot. Environ 1991, 109: 59-68.

29. Joesten V, Schaad L. Hydrogen Bonding Marcel Dekker, Inc., New York 1974.

30. Vinogradov S, Linnell R. Hydrogen Bonding. Reinhold, New York, 1971

31. Chickos J, Braton C, Hesse D, Liebman J. Estimating entropies and enthalpies of fusion of organic compounds. J. Org. Chem 1991(56): 927-938

32. Chickos J, Acree W, Liebman J. Estimating Solid–Liquid Phase Change Enthalpies and Entropies. J. Phys. Chem. Ref. Data 1999 (28): 1535-1674

December 21, 2017   10:14 PM

33. Coutsikos P, Voutsas E, Magoulas K, Tassios, D. Prediction of vapor pressures of solid organic compounds with a group-contribution method. Fluid Phase Equilib. 2003, 7(1-2): 263-281

34. Trouton F. On Molecular Latent Heat. Phil. Mag.1884(**18**): 54–57.

35. Walden P. Uber die Schmeltzwarme, Spezifische Kohasion und Moleculargrosse bei die Schmeltztemperatur. Z. Elektorchem. 1908(14): 713-728.

36. Yalkowsky S. Estimation of entropies of fusion of organic compounds. *Ind. Engin. Chem., Fundam.* 1979 (**18**): 108-111.

37. Dannenfelser R, Surendran N, Yalkowsky S. Molecular Symmetry and Related Properties. SAR QSAR Environ. Res 1993(1): 273-292.

38. Johnson J, Yalkowsky S. Two New Parameters For Predicting The Entropy Of Melting: Eccentricity (E) And Spirality (M). *Ind. Eng. Chem. Res.*, 2005, 44 (19), Pp 7559–7566

39. Leclercq M, Collet A, Jacques J. Etude des d'antipodes optiques—XII, Mesure de la stabilite des racenique vrais. Tetrahedron, 1976 (32): 821-838.

40. Hartley C. Folding or ortho-phenylenes. Accounts Chem. Res.2016(49): 646-654.

41. Tsakanikas P, Yalkowsky S. Estimation of Melting Point of Flexible Molecules: Aliphatic Hydrocarbons. Tox. Env. Chem 1988(17): 19.

42. Dannenfelser R, Yalkowsky S. Estimation of Entropy of Melting from Molecular Structure: A Non-Group Contribution Method. Ind. & Eng. Chem. Res. 1996(35): 1483-1486.

43. Wunderlich B. Macromolecular Physics, Volume 3, Crystal Melting. Academic Press New York 1980

44. Richard J. Relations between the melting points and the latent heats of fusion of the metals. Chem. News 1897 (75): 278.

45. Chickos J, Nichols G. Simple Relationships for the Estimation of Melting Temperatures of Homologous Series. *J. Chem. Eng. Data*, 2001, 46 (3): 562–573

46. Broadhurst, M., J. Res., Nat'l Bur. Stand, USA 1962(66A): 241-249.

47. Flynn G, and Yalkowsky, S. Correlation and Prediction of Mass Transport Across Membrane I: Influence of Alkyl Chain Length on Flux Determining Properties of Barrier and Diffusant," J. Pharm. Sci. 1972(61): 838-852.

48. Yalkowsky S, Flynn G, Slunick T. Importance of Chain Length on Physicochemical and Crystalline Properties of Organic Homologs, J. Pharm. Sci., 1972(61): 852-857.

49. Gavezzotti A. Molecular symmetry, melting temperatures and melting enthalpies of substituted benzenes and naphthalenes, J. Chem. Soc, Perkin Trans 1995(2): 1399-1404.

50. Ferguson L. Eloctronegativity And Electric Dipole Moments. The Modern Structural Theory Of Organic Chemistry, New Jersy: Prentice-Hall,Inc.; 1952:199

51. Hildebrand J, Scott R. The Solubility of Nonelectrolyte, 3rd ed, NewYork: Reinhold Publishing Company.; 1950: 58

Captions

Figure 1. Hypothetical Two Dimensional Packing Arrangements for Carbon Dioxide. A: maximum packing efficiency, b: maximum dipolar interactions, c: maximum total interactions

Figure 2. Possible two dimensional arrangements for a water molecules. A: maximum hydrogen bonding, b: maximum dipolar interaction, c: maximum dispersion interaction.

Figure 3. Schematic of hydrogen bonding geometry. (Not to scale)

Figure 4. Reinforced hydrogen bonds, MHBN is the maximum hydrogen bond number

Figure 5. Heat of fusion (KJ/mol): □, Entropy of fusion(J/mol.K): △, and Kelvin Melting Temperature: ○, of the normal alkanes.

Figure 6. Heats of fusion(KJ/mol) , □ and entropies of fusion (J/mol.K) , △ of normal alkenes.(Aromatic carbons are not included.)

Figure 7. Heats of fusion (KJ/mol), □ and entropies of fusion (J/mol.K), △ of alkylbenzenes. (Aromatic carbons are not included.)

Figure 8. Heats of fusion (KJ/mol) of polymethylbenzenes. (Aromatic carbons are not included.)

Figure 9. Heats of fusion (KJ/mol) of cycloalkanes

Figure 10. Heats of Fusion(KJ/mol) of Polycyclic Aromatic Hydrocarbons.

Figure 11. Rotational symmetry numbers for some representative compounds. Note that the symmetry number used here is based upon rotation, the only symmetry operation that can physically be performed on a molecule, and does not count mirror planes or operations that cannot be physically performed. Therefore, conical, cylindrical, and spherical compounds are not designated as equal to unity as in chemistry. Rather they are assigned arbitrary high values of 20 to indicate that they are more symmetrical than neopentane or benzene and that they have at least one infinite rotational axis. (From Dannenfelser et al [37]).

Figure 12. Melting points of some isomeric and near isomeric hydrocarbons(^{o}C)

Figure 13. Illustration of chirality in aromatic compounds

Figure 14. *Potential energy vs torsional angle in butane. Note that the trans conformation, designated as anti, is the slightly more stable than the gauche conformations*
From Chemistry Stack Exchange

Figure 15. Kelvin melting points of alkanes vs. reciprocal chain length.

Figure 16. Reciprocal Kelvin melting points of alkanes vs. reciprocal chain length.

Figure 17. Effect of alkyl chain length on aromatic compounds. α: Alpha-alkylnapohthalenes, β: beta-alkylnaphtrhalenes, Φ: alkylbenzenes. (The alkanes are included as a reference.)

Figure 18. Effect of alkyl chain length on the melting points of some dipolar and hydrogen bonding homologs.

Figure 19. Melting points of disubstituted naphthalenes as a function of substituent positions. Modified from Gavezzotti[49]

Figure 20. Experimental versus calculated melting temperature (K). N = 2044, R2 = 0.81

Table 1: Group and bond polarizabilities (cm^3*10^{-24})

Group contributions*		Bond contributions **	
−C	0.93	C–C	0.48
−H	0.42	C–H	0.58
−O	0.64		
−OH	0.59		
−N	1.03	C≡N	1.40
−NH	0.93	N–H	0.84
−NH$_2$	0.87		
−F	0.38		
−Cl	2.28	C–Cl	2.08
−Br	3.34	C–Br	2.88
−I	5.11		
−C=C db	0.58 + Carbons	C=C	1.06
−C≡C tb	0.86 + Carbons	C≡C	1.27
=O	0.84	C=O	0.75
−C$_6$H$_5$	9.38		

*Reference number 50
** Reference Number 51

Table 2. Environmental designations of UPPER groups

Designation Description

Designation	Description
X	bonded only to sp^3 hybrid atoms
Y	bonded to only one sp2 hybrid atom (aromatic or vinyl)
Z	bonded to one sp atom
YY	bonded to two sp2 carbons
rg	designates an atom or group in a saturated ring
fu	designates an bridgehead atom contained in two saturated rings
ar	designates an atom or group within an aromatic ring system
ar2	designates a bridgehead atom contained in two unsaturated rings
ar3	designates a bridgehead atom contained in three unsaturated rings
bip	designates a central carbon in a biphenyl type structure

Table 3. Primary group contributions (m_i values) for calculation of the heat of melting

Group	Group Environment								
	X	Y	YY	RG	FU	ar	br1	br2	bip
-CH$_3$	0.701	1.221	--	--	--	--	--	--	--
-CH$_2$	1.408	0.331	-2.524	1.054	--	--	--	--	--
-CH$_2$*	3.807	--	--	--	--	--	--	--	--
-CH	1.875	-0.916	-2.749	1.046	1.695	1.235	--	--	--
-C	1.219	-1.125	--	0.757	1.301	1.777	1.329	-0.564	2.602
=CH$_2$	--	0.402	--	--	--	--	--	--	--
=CH	--	1.710	1.689	0.883	--	--	--	--	--
=C	--	2.337	0.655	1.362	--	--	--	--	--
=C=	--	--	2.058	--	--	--	--	--	--
-F	-0.087	0.409	--	--	--	--	--	--	--
-Cl	1.889	1.581	--	--	--	--	--	--	--
-Br	4.674	2.911	--	--	--	--	--	--	--
-I	4.034	4.334	--	--	--	--	--	--	--
-CO	8.037	3.332	--	--	--	--	--	--	--
-CHO	--	5.470	--	--	--	--	--	--	--
-CN	5.714	6.558	--	--	--	--	--	--	--
-NO$_2$	--	4.584	--	--	--	--	--	--	--
-COO	9.488	6.208	--	--	--	--	--	--	--
-OCO	--	7.568	--	--	--	--	--	--	--
-OCOO	--	5.335	--	--	--	--	--	--	--
-O	2.921	3.162	-6.918	--	--	-0.922	--	--	--
-S	--	5.313	--	--	--	--	--	--	--
-N	--	2.013	--	--	--	--	--	--	--
-OH	4.953	6.699	--	--	--	--	--	--	--
-SH	--	2.635	--	--	--	--	--	--	--
-NH	1.181	3.799	--	--	--	--	--	--	--
-NH$_2$	6.884	5.681	--	--	--	--	--	--	--
-COOH	14.287	11.785	--	--	--	--	--	--	--
-NHCO	--	8.167	--	--	--	--	--	--	--
-NHCOO	--	6.929	--	--	--	--	--	--	--
-NHCONH$_2$	--	14.865	--	--	--	--	--	--	--
-NHCON	--	16.721	--	--	--	--	--	--	--
-CONH$_2$	13.418	12.814	--	--	--	--	--	--	--

CH$_2$* = methylene group bonded to two unbranched CH$_2$ atoms.
- Data source: Reference Number 26

Table 4: Reduction of A–H···B distance due to hydrogen bonding

H-bond Atoms	AH--B distance observed	AH--B distance van der Waals	Reduction of Distance
F–H$\cdots$F H	2.26	3.49	1.23
O–H$\cdots$O	2.72	3.04	0.32
O–H$\cdots$O$^-$	2.75	3.04	0.29
O–H$\cdots$N	2.78	3.07	0.29
O–H$\cdots$S	3.31	3.32	0.01
O–H--F	2.72	2.92	0.20
O–H--Cl	3.12	3.28	0.16
O–H--Br	3.28	3.37	0.09
O–H--I	3.53	3.48	0.05
N–H--O	2.93	3.07	0.14
N–H--O$^-$	2.98	3.07	0.08
N–H--N	3.07	3.10	0.03
N–H--S	3.39	3.35	-0.04
O–H--F	2.92	2.95	0.03
O–H--Cl	3.23	3.31	0.08
O–H--Br	3.37	3.40	0.03
O–H--I	3.66	3.51	-0.15

Table 5: Reduction of Hydrogen bond H···B distance due to hydrogen bonding

H-bond	observed	van der Waals	Reduction of
Atoms	*H···B distance*	*H···B distance*	*H···B Distance*
F–H···F	1.22	2.35	1.13
O–H···O	1.7	2.6	0.9
O–H···N	1.9	2.7	0.8
C–H···O	2.3	2.6	0.3
N–H···O	2.0	2.6	0.6
N–H···N	2.2	2.7	0.5
N–H···S	2.3	2.6	0.3

Data source: References Number 28 and 29

Table 6: Melting points of linear and cyclic analogs

Linear Analog	MP	Ref	Cyclic Analog	MP	Ref	Dif
n-butane	-138	26	cyclobutane	-91	26	47
n-pentane	-130	26	cyclopentane	-94	26	36
n-hexane	-95	26	cyclohexane	7	26	102
n-heptane	-91	26	cycloheptane	-8	26	83
n-octane	-57	26	cyclooctane	15	26	72
dimethyl ether	-142	26	ethylene oxide	-112	NIST*	30
diethyl ether	-132	26	tetrahydrofuran	-109	NIST*	32
diethyl sulfide	-104	NIST*	tetrahydrothiophene	-99	NIST*	5
dimethyl amine	-93	NIST*	ethylenimine	-78	NIST*	15
diethyl amine	-50	NIST*	pyrrolidine	-61	NIST*	-11
3-pentanone	-40	NIST*	cyclopentanone	-51	NIST*	-11
diethyl sulfone	70	NIST*	sulfolane	28	NIST*	-42
ethyl acetate	-80	NIST*	butyrolactone	-45	NIST*	35
dimethyl carbonate	7	NIST*	ethylene carbonate	37	NIST*	30
acetic anhydride	-73	NIST*	succinic anhydride	120	NIST*	193

*NIST: National Institute of Standards and Technology chemical webbook

Table 7. Melting Points(^{o}C) of polymethyl and poly dipolar benzenes

Substituent positions	Methyl Benzenes CH$_3$	Chloro Benzenes Cl	Bromo Benzenes Br	Iodo Benzenes I	Nitro Benzenes NO2	Methoxy Benzenes OCH3
Benzene	6	6	6	6	6	6
mono-	-95	-45	-31	-31	8	22
1,2-di-	-25	-17	7	24	118	-35
1,3-di-	-48	-24	-7	35	89	22
1,4-di-	13	53	87	129	173	-
1,2,3-tri-	-23	54	88	116	-	-
1,2,4-tri	-45	17	44	92	-	-
1,3,5-tri-	-48	63	122	184	115	-
1,2,3,4-tetra-	-8	47	58	136	-	-
1,2,3,5-tetra-	-24	51	97	148	-	-
1,2,4,5-tetra-	79	139	180	254	-	-
penta-	54	85	160	172	-	-
hexa-	166	228	327	350	-	-

Data source: Reference number 26

Table 8 **Melting Points of poly hydrogen bonding benzenes**

Substituent positions	Hydroxy Benzenes	Amino Benzenes	Carboxy Benzenes	Amido Benzenes
	OH	NH$_2$	COOH	CONH$_2$
Benzene	6	6	6	6
mono-	41	-6	122	129
1,2-di	105	102	199	-
1,3-di	110	63	345	286
1,4-di	170	140	-	346
1,2,3-tri	130	103	179	-
1,2,4-tri	140	98	238	-
1,3,5-tri	218	-	380	-
1,2,3,4-tetra	-	241	311	-
1,2,3,5-tetra	-	-	308	-
1,2,4,5-ttra	-	-	-	-
Penta	-	238	-	-

Data source: Reference number 26

a   b   c

a   b   c

Sum of A and B covalent radii

Sum of A and B van der Waals radii

A

H

NONE WEAK STRONG WEAK NONE

B

MHBN=2

MHBN=4

Normal Alkanes

n-Alkenes

Property value vs Number of Carbons

Cycloalkanes — scatter plot of Heat of Fusion (KJ/mol) versus Number of Carbons.

-130   -160   -20   -94

-96   -153   -128   6

-57   -110   100   14

-108   -139   -141   -150
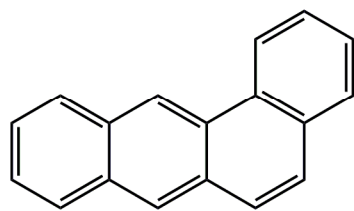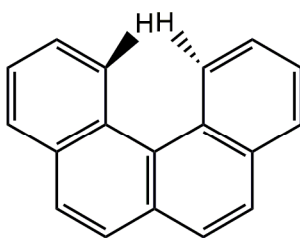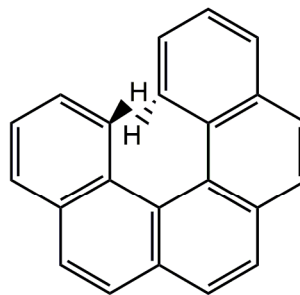
81   227   100   218

-62   116   254   357
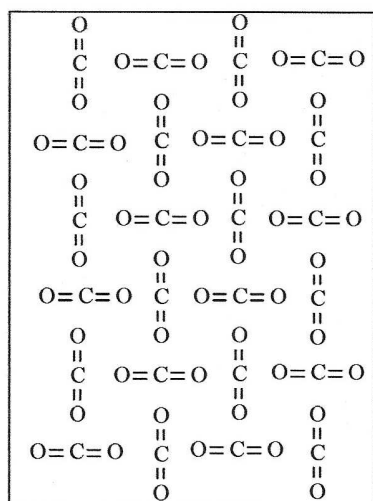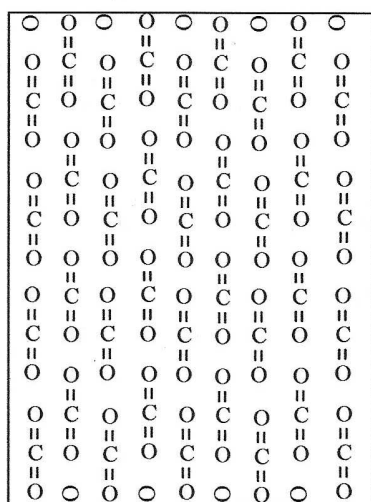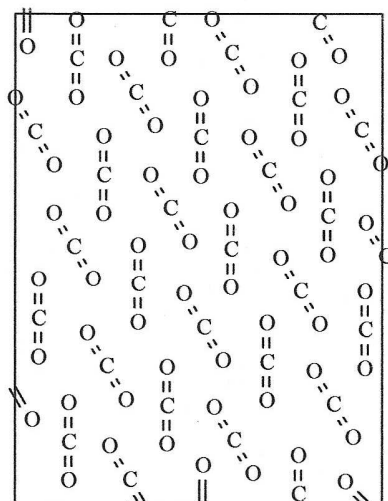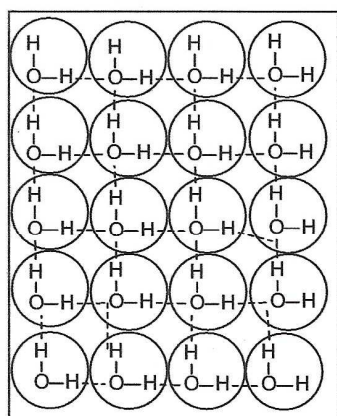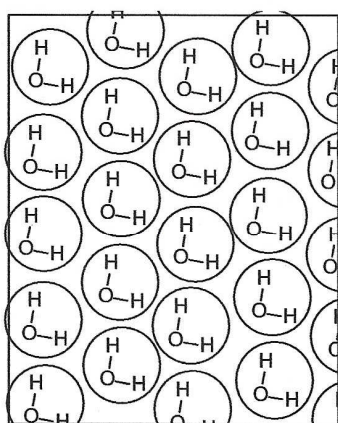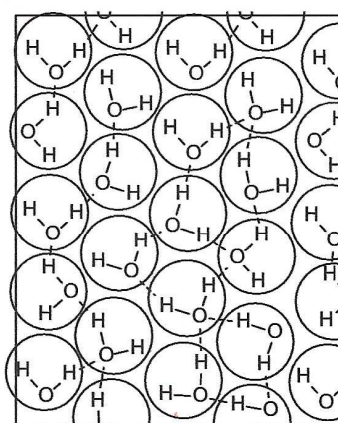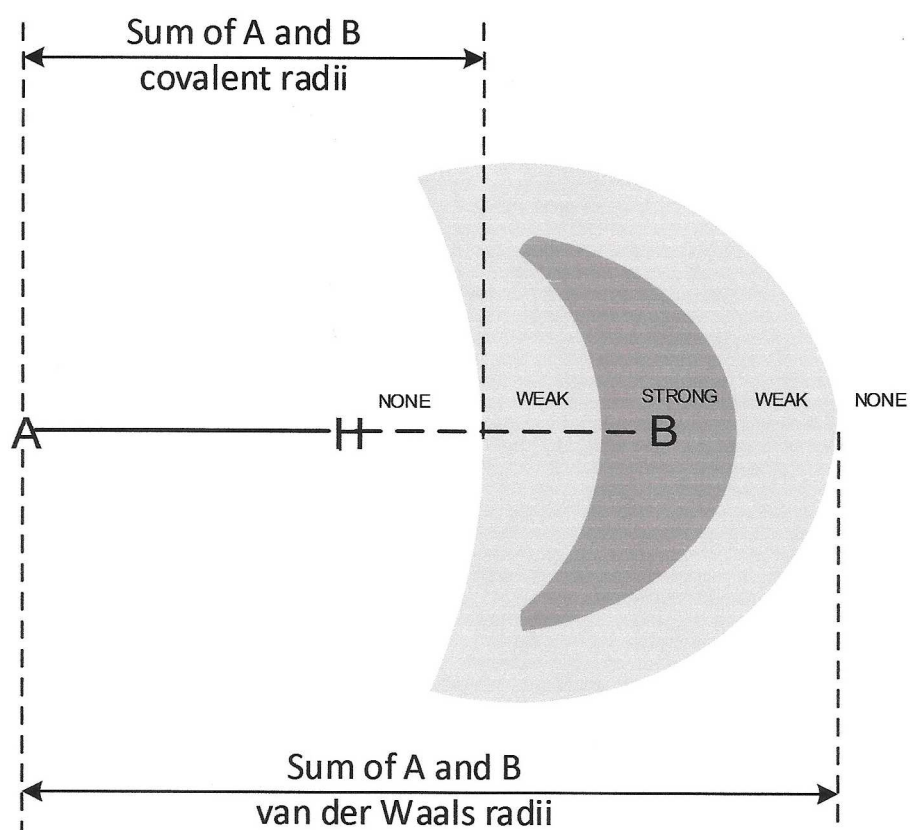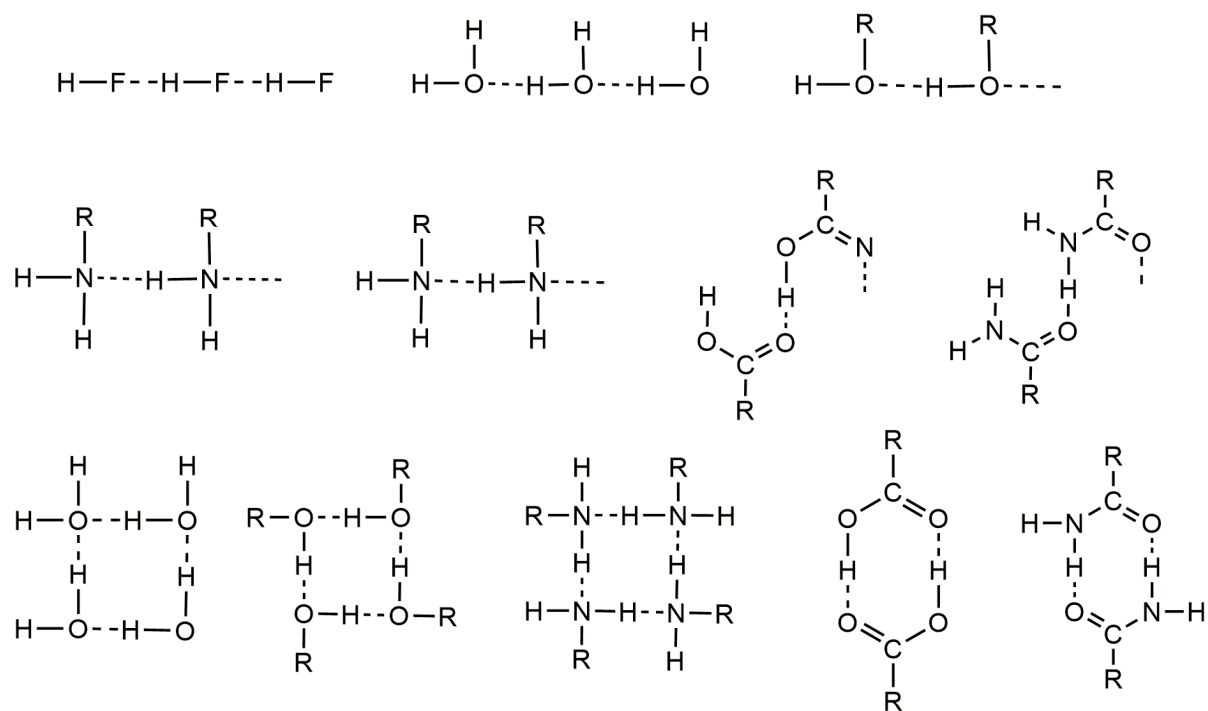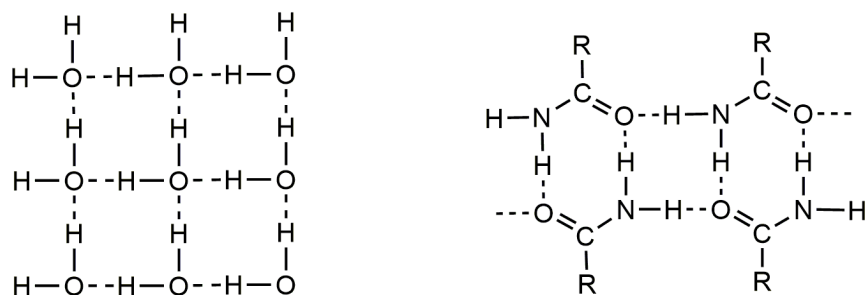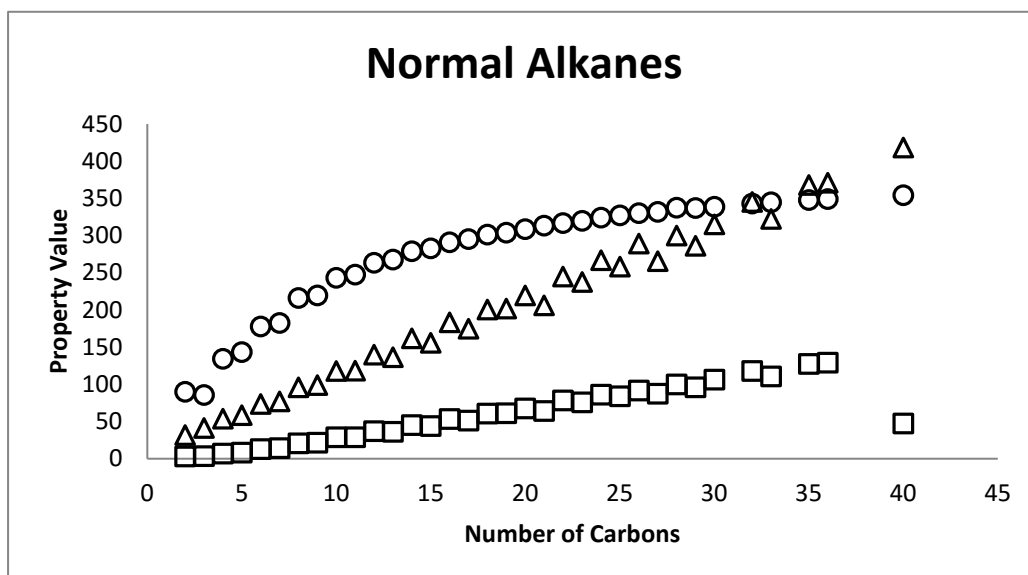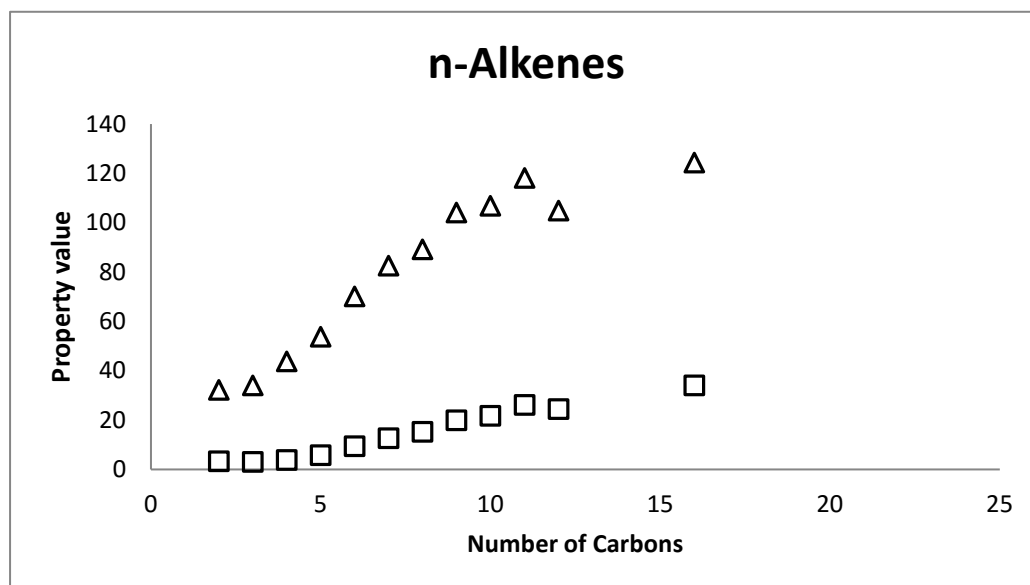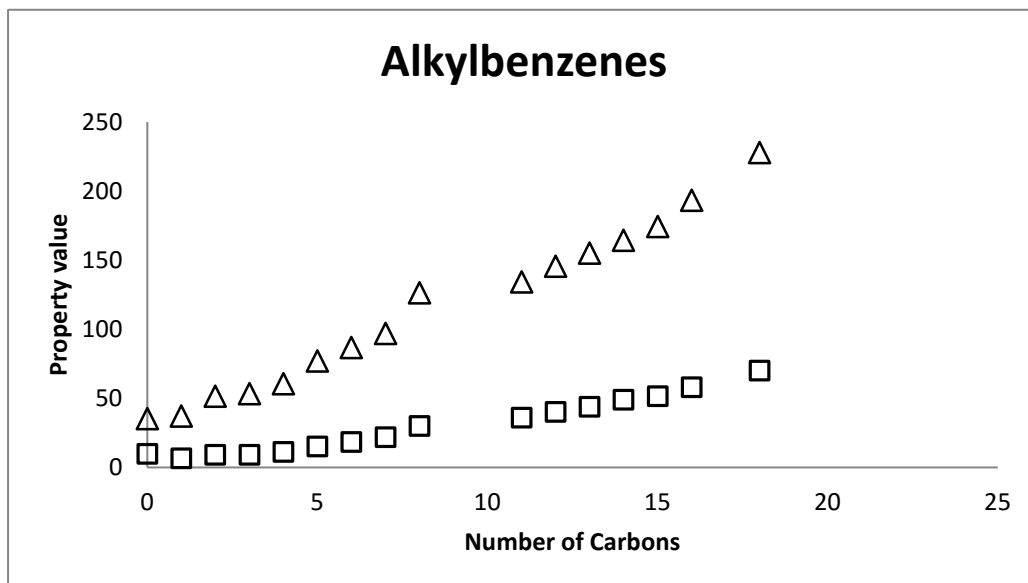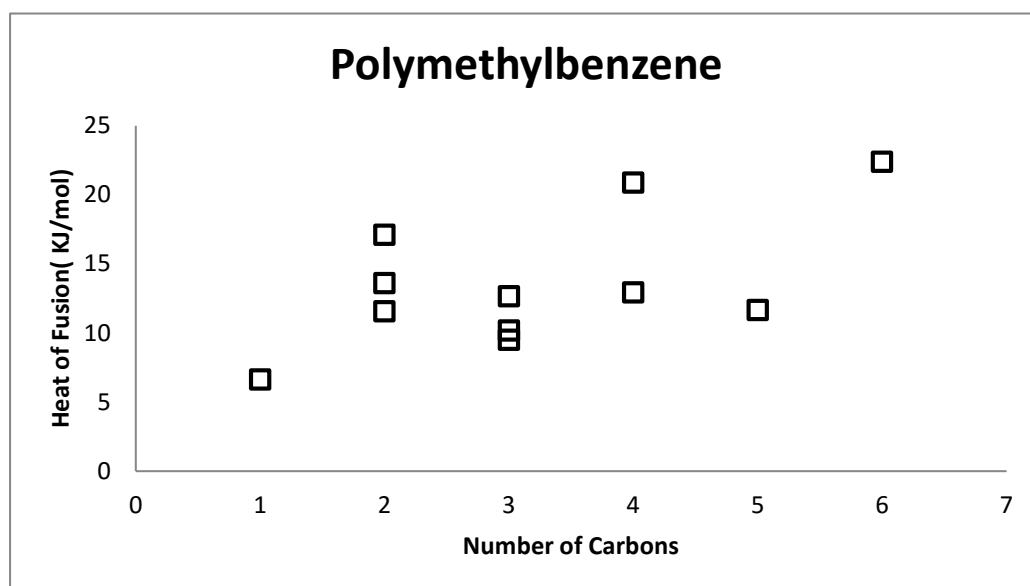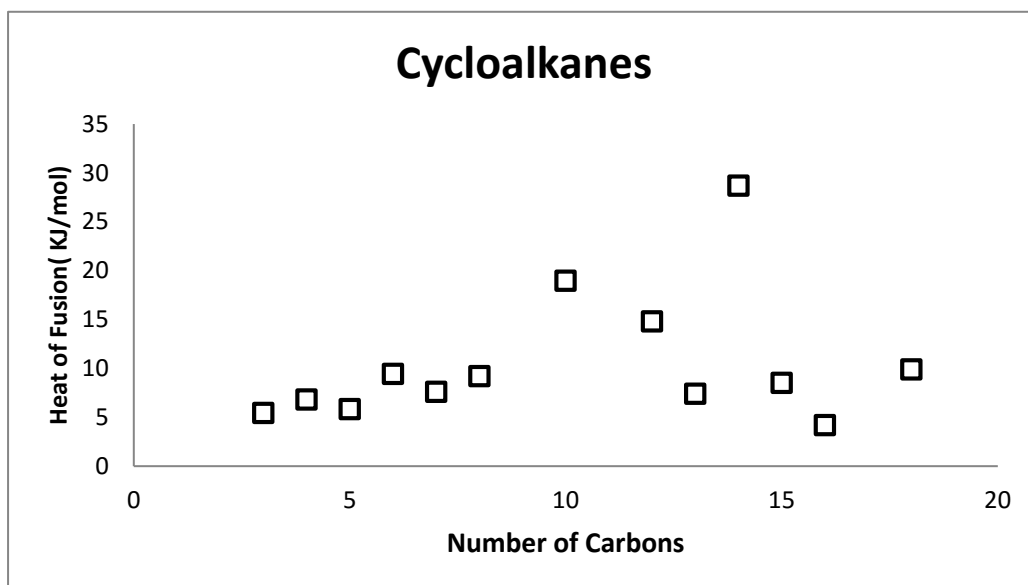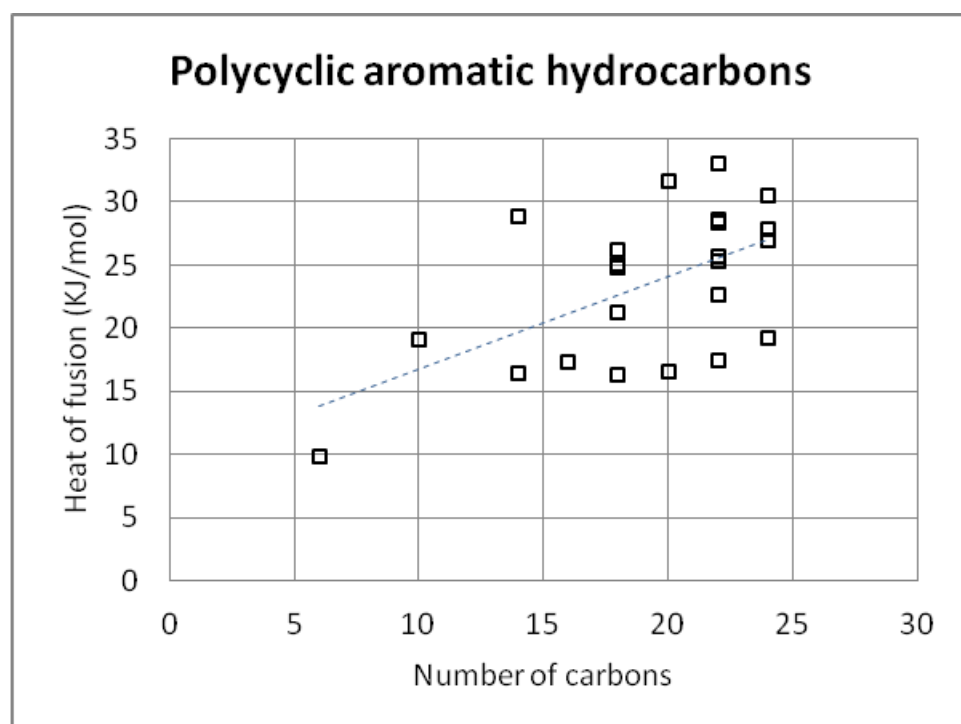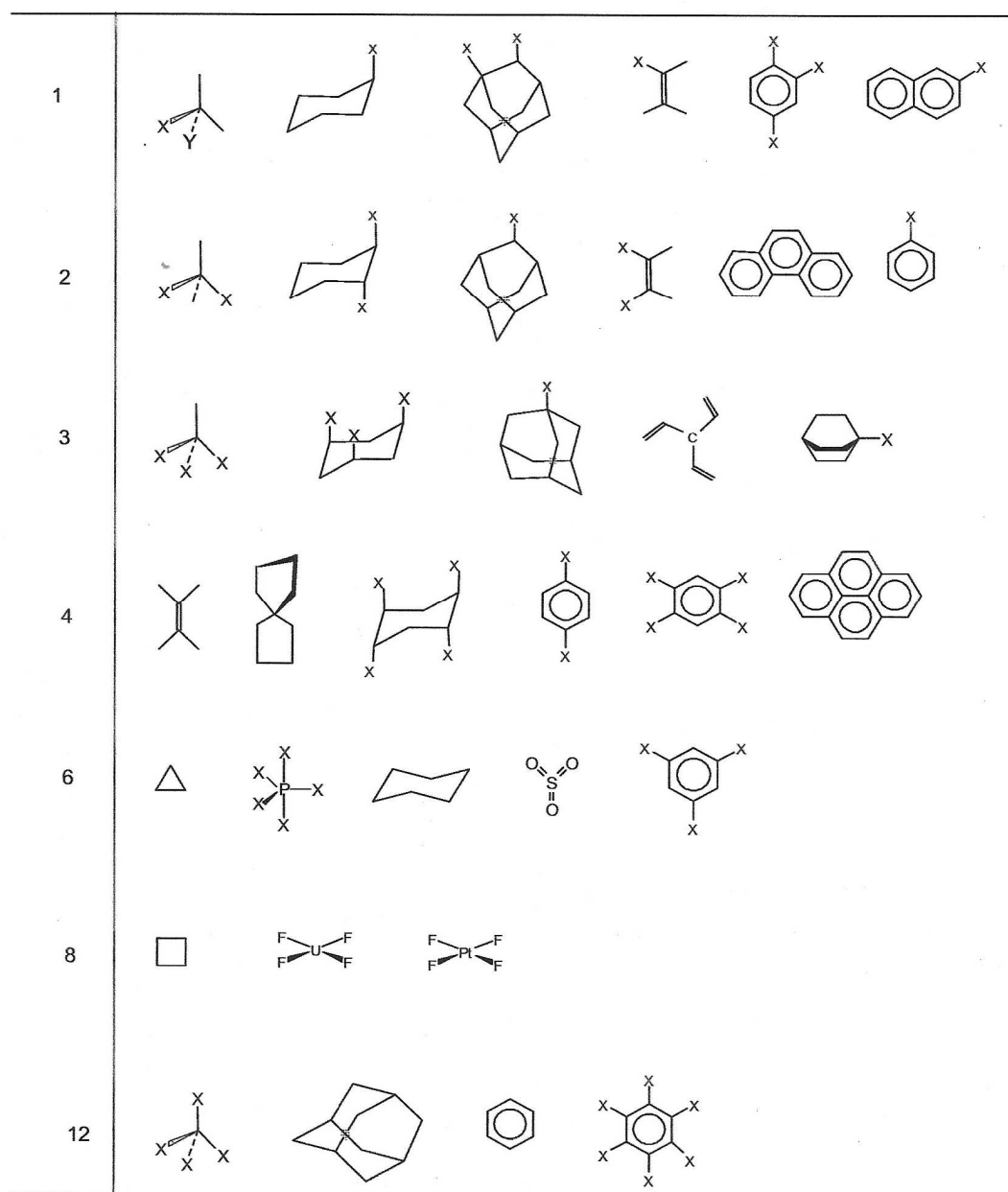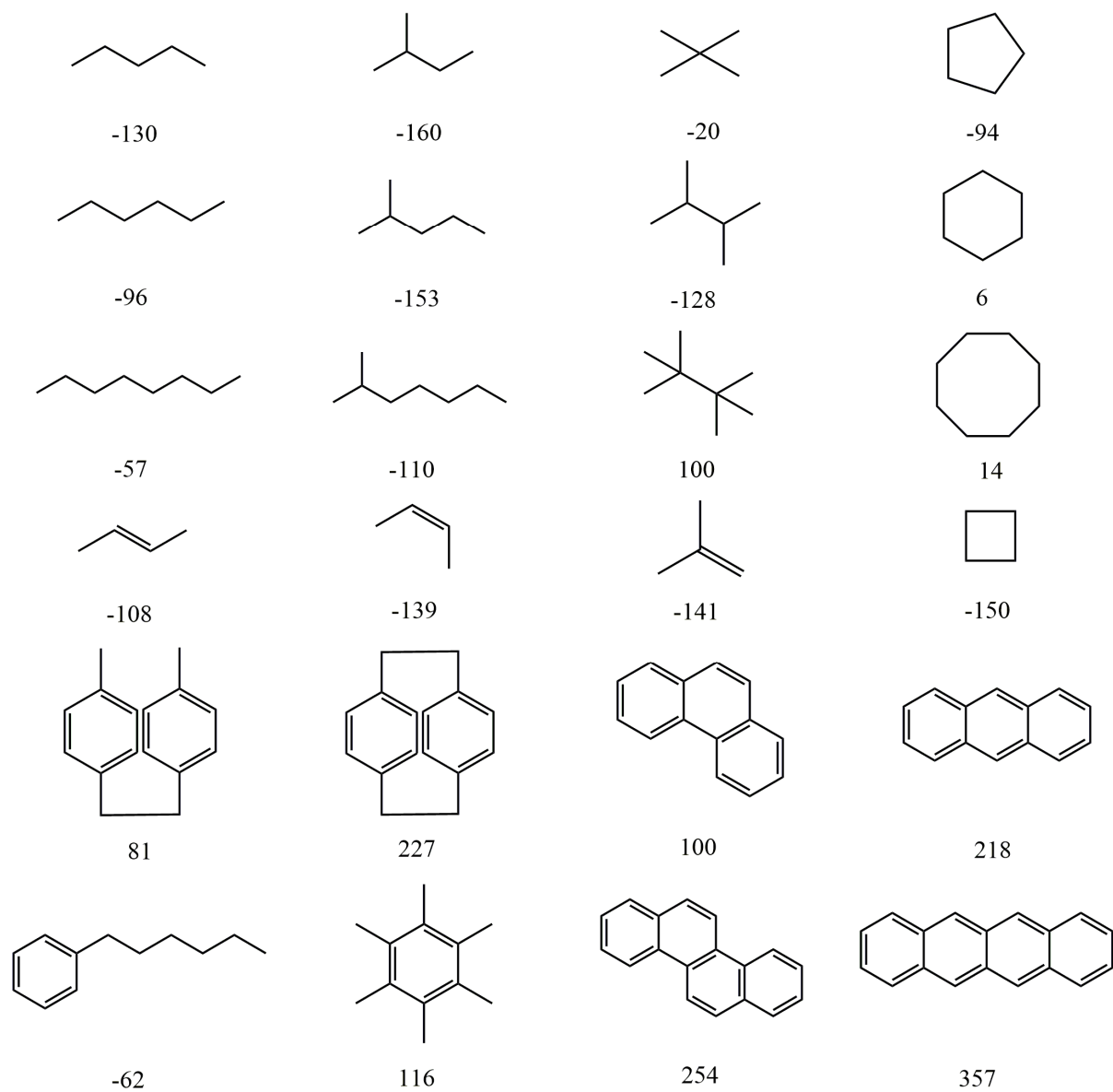
1, 2,-benzanthracene   1,2-benzphenanthrene   1,2,9,10-dibenzphenantrene

Normal Alkanes

y = -1825.7x + 400.14

Melting Temperature(K)

1/no. of carbons

Normal Alkanes

y = 0.0153x + 0.0024

Alkyl Homologs

Melting Temperature