The Entropy of Fusion
and
Quantitative Structure-Property Relationship (QSPR)

Objectives
You will use multiple linear regression to predict the value of the entropy of fusion of a compound based on its structure. You will then determine the value experimentally using differential scanning calorimetry (DSC), and compare your two values.

Introduction
QSAR and QSPR
Quantitative structure-activity relationship, QSAR, is a statistical method that is used to develop a predictive model for the biological activity of a drug as a function of its structural properties. The goal in a QSAR experiment is to develop an explicit form of eq. 1:

\[ B = B(p_1, p_2, \ldots) \]  \hspace{1cm} \text{Equation 1}

Here \( B \) is biological activity (an enzyme inhibition constant, for instance) and \( p_i \) are the values of parameters that describe the structure of the molecule (for instance, molar mass, dipole moment, or number of hydrogen bond acceptors). These parameters are called descriptors. This concept can be broadened to encompass properties other than biological activity. In this case, we refer to a quantitative structure-property relationship, QSPR. The goal in a QSPR study is to develop an explicit form of eq. 2:

\[ F = F(p_1, p_2, \ldots) \]  \hspace{1cm} \text{Equation 2}

Here \( F \) is physical property such as melting point. In this experiment, we will use the QSPR technique to develop an equation relating the entropy of melting and structural descriptors of a molecule.

The entropy of fusion
The entropy of a compound is given by eq. 3:

\[ S = k_B \ln W \]  \hspace{1cm} \text{Equation 3}

Here, \( k_B \) is Boltzmann’s constant and \( W \) is the number of microstates that comprise the macrostate of the system. An accurate calculation of \( W \) requires detailed knowledge of the vibrational, rotational, and translational quantum states of the system, but we can estimate the entropy change that occurs during melting using some simple rules.
The entropy of a compound increases when it melts, because liquids have more modes of motion, and therefore a higher value of \( W \). We can break these modes into several categories:

\[
\Delta_{\text{flus}} S = \Delta S_{\text{expansion}} + \Delta S_{\text{orientation}} + \Delta S_{\text{conformation}} \tag{Equation 4}
\]

Let us examine each of the terms on the right-hand side of Eq. 4.

Liquids generally have lower density than the corresponding solids, and so there is greater separation between molecules. This decreases the strength of the intermolecular forces, and opens up new intermolecular vibrational modes, thus increasing the value of \( W \). We will refer to the ensuing increase in entropy as \( \Delta S_{\text{expansion}} \). Prediction of \( \Delta S_{\text{expansion}} \) requires detailed knowledge of the geometry of the solid state, and so we will not attempt to model \( \Delta S_{\text{expansion}} \).

Molecules in the liquid state can rotate though different orientations, while in the solid state they cannot. We will refer to the entropy increase due to rotation as \( \Delta S_{\text{orientation}} \). One might assume that all molecules would have similar values of \( \Delta S_{\text{orientation}} \), but this is not so. Symmetric molecules can adopt more than one indistinguishable orientation. For instance, \( \text{NH}_3 \) has three indistinguishable orientations. Only distinguishable orientations contribute to \( W \), so symmetrical molecules have a smaller value of \( \Delta S_{\text{orientation}} \). We quantify symmetry with the external symmetry number, \( \sigma_e \). The external symmetry number is the number of indistinguishable orientations that a molecule can adopt.

Molecules with rotatable bonds can undergo internal rotations as they move from one conformation to another. We will refer to the entropy increase due to conformational change as \( \Delta S_{\text{conformation}} \). The value of \( \Delta S_{\text{conformation}} \) increases with the number of rotatable bonds in the molecule. Let us define \( \tau \) as the number of rotatable bonds in a molecule. For our purposes, we will consider a bond rotatable only if it fulfills three criteria: it is not in a ring, it is between two non-terminal atoms of the carbon skeleton, and it is a single bond. For instance, the middle bond in butane is rotatable, while the two bonds to the methyl groups are not. Molecules with high values of \( \tau \) will have high values of \( \Delta S_{\text{conformation}} \). However, symmetry plays a role here, too. Rotation about a rotatable bond can lead to indistinguishable rotamers; these rotamers do not contribute to \( \Delta S_{\text{conformation}} \). We can account for this

\[\quad \text{by using the external symmetry number, } \sigma_e. \]

\[\quad \text{This is true of most solids. However, some compounds undergo a transition to a plastic crystal phase, in which the molecules rotate freely, but do not undergo translational motion.} \]

\[\quad \text{The molar entropy of this phase will be lower than the liquid phase, but higher than the solid phase.} \]

\[\quad \text{The small entropy of fusion for symmetrical compounds increases their melting points. The empirical observation that symmetric compounds tend to have high melting points is known as Carnelly's rule.} \]

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internal symmetry by introducing the internal symmetry number, \( \sigma_i \). For instance, \( \sigma_i = 3 \) for 2,2,3,3-tetramethylbutane, because the 3 rotamers of the compound are indistinguishable. Thus, increasing \( \sigma_i \) decreases \( \Delta S_{\text{conformation}} \). Note that we will only be checking for internal symmetry on rotatable bonds. The overall effect of symmetry is the product of internal and external symmetry:

\[
\sigma = \sigma_i \cdot \sigma_e
\]

Equation 5

Finally, even molecules with no rotatable bonds tend to become flexible if they are large enough, so we expect that there might be some dependence on the molecular size. Let’s include the parameter \( n \), the number of carbon atoms in the molecule, in our fit.

The goal of this experiment is to find an explicit version of equation 6.

\[
\Delta_{\text{fus}} S = \Delta_{\text{fus}} S(n, \sigma, \tau)
\]

Equation 6

**Differential scanning calorimetry**

Differential scanning calorimetry is a technique that can be used to determine the heat capacity as a function of temperature. The enthalpy, entropy, and temperature of phase transitions can be calculated from the heat capacity data produced by the DSC. In the basic DSC experiment, a sample and a reference material are both heated over a specified temperature range. The reference is chosen so as not to have any thermal transitions in the temperature range of interest. In practice alumina, or just an empty sample pan, is used. The sample and reference each have their own heater, and the power to the heaters is adjusted so there is no temperature difference between sample and reference throughout the temperature range. The difference in power supplied to the two heaters is measured as the temperature is scanned.

When the thermal transition is first order, which is the case for melting, the maximum heat capacity corresponds to the transition temperature. Using the following equation:

\[
\Delta H_{\text{cal}} = \int_{T_1}^{T_2} C_p dT
\]

Equation 7

The enthalpy of the transition can be calculated. From these results the entropy of transition can be calculated:

\[
\Delta_{\text{fus}} S = \frac{\Delta H_{\text{cal}}}{T_m}
\]

Equation 8
Procedure

Differential scanning calorimetry
Each student will prepare one sample. The first team will prepare samples of naphthalene, and the second team will prepare samples of tridecane. At the end of class, the two teams will exchange data.

Sample preparation
Each student will prepare a naphthalene pan in the following manner:

1. Using forceps, place a sample pan and lid on the analytical balance, and tare the balance. Place the pan on the pan-holder. Do not use a weigh boat for this or subsequent steps, as they can carry static charge, which will make the weight inaccurate.
2. Place the micro-funnel on the sample pan. Add enough naphthalene to fill the pan half full. Use the micro-pestle to gently push the naphthalene into the pan. Remove the micro-funnel, and use the micro-pestle to brush off any naphthalene on the top edge of the pan. The edge must be absolutely clean to form a tight seal with the lid. Cover with the lid.
3. Place the pan-holder in the pan press and press the pan.
4. Weigh the sealed pan.
5. Load each pan on the autosampler immediately.

Read these instructions, and press your first pan under your instructor’s direct supervision. Each student will prepare a tridecane pan in the following manner:

1. Using forceps, place a sample pan and lid on the analytical balance, and tare the balance. Place the pan on the pan-holder. Do not use a weigh boat for this or subsequent steps, as they can carry static charge, which will make the mass reading inaccurate.
2. Rinse the gas-tight syringe 3 times with tridecane, and then use it to add about 20 μL of tridecane to the pan. Cover with the lid.
3. Place the pan-holder in the pan press and press the pan.
4. Weigh the sealed pan.
5. Load the first pan on the autosampler immediately.

Instrumental procedure

1. Log in to the computer with username METTLER. There is no password.
2. Open the STARe software.
3. Check to make sure that the autosampler is not about to load a sample. If the autosampler is active, the dust cover must not be removed.
4. Place a tridecane pan in an empty space in the autosampler. For naphthalene samples, select File>Open Method> chem 354 naphthalene 2, which is the method file for this experiment. For tridecane samples, select File>Open Method> chem 354 tridecane, which is the method file for this experiment.

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5. Enter the mass of the sample (don’t include the mass of the pan or lid), the sample name, and the position in the autosampler. Note that the number you enter will be 100 plus the number indicated on the carousel, so position 7 is really position 107.

6. Click on Send Experiment.

7. Watch the robot load the sample to ensure that it loads properly.

8. To monitor your experiment in real time, click on another experiment, and then back on yours. A graph showing your thermogram will appear. This also will show you the time left for your experiment and for all the experiments in the queue.

9. While samples are running, press the remaining pans. After pressing them, repeat steps 1-4 to put them into the instrument queue.

10. While your last sample is running, start analyzing the previous experiments. To retrieve your data, go to Session>Evaluation Window

11. Open File>Open Curve, and select one of your experiments

12. Select the last melting peak on the thermogram by dragging a box around it with your cursor.

13. Press control-F6 to integrate the peak.

14. Record the onset temperature (melting point) and the enthalpy of fusion. Note the units—you will need to convert the results to kJ/mol.

**Multiple linear regression**

1. Download the training set data from PolyLearn or the website.

2. Fit the training set data to the functional form

\[
\Delta_{fu}S = c_0 + c_1 n + c_2 \tau + c_3 \sigma + c_4 \varepsilon
\]

Equation 9

The last term in the equation represents the experimental error present in the entropy measurement for each compound in the training set. Because \( \varepsilon \) is function of experimental error, it is not included in the regression analysis. (You may wish to consult the handout Curve Fitting in MATLAB.)

3. Record the values for the slopes \( c_1, c_2, c_3, \) and the y-intercept \( c_0 \). Also, record the standard errors for these numbers.

4. Use the values of \( c_1, c_2, c_3, \) and the y-intercept \( c_0 \) to calculate a theoretical value for the entropy of fusion for each molecule in the training set. Graph these values as a function of the empirical values.

5. Determine values for \( \sigma, \tau \) and \( n \) for your molecules.

6. Plug these values into eq. 9 to calculate a theoretical value for the entropy of fusion for your molecules (and the uncertainty), and compare it to the experimental value.
7. Look up the literature value for \( \Delta_{fus}S \) on the NIST webbook and compare it to your experimental and theoretical values.

**Required Report Elements**

1. The values for \( c_0, c_1, c_2, \) and \( c_3. \) Also, report the error limits for these numbers.

2. Theoretical values of the entropy fusion graphed as a function of the empirical values for the compounds in the training set.

3. The theoretical values for the entropy of fusion of both compounds you tested on the DSC, and the associated uncertainty.

4. The experimental values for the melting temperature and entropy of fusion of both compounds, and the associated uncertainty.

5. The literature values for the melting temperature and entropy of fusion of both compounds.

**References**


