Exercise 10

The goal of this exercise is to calculate the partition constant of caffeine from molecular dynamics simulations.

The partition constant of a compound is the ratio of its concentrations in the two phases of a mixture of two immiscible liquids at equilibrium. In general, it is determined from the distribution between water and n-octanol. It gives a measure of a substances hydrophilicity/hydrophobicity. It is widely used in pharmaceutical research in order to estimate the distribution of a substance throughout the body. There, the partition constant is one of the most important properties of a compound used to identify candidate substances in early stages of the drug discovery process. In environmental research, the partition coefficient is used to predict the uptake of the substance by e.g. groundwater or animals, and to model migration pathways of a substance in the environment.

The partition constant is defined as the ratio of the concentrations; for partition between water and octanol:

$$P_{\text{ow}} = \frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{water}}} \tag{1}$$

As such it can be calculated from the difference in solvation free energies of the substance in the two solvents.

Commonly, the decadic logarithm of the partition constant is found in literature (simply denoted as $\log P$).

Decide on a method how to calculate the change in solvation free energy. You are free to use any method you want (you can start from the files used in the previous exercise). Topology files for caffeine and octanol are found in the `Ex10.tar.gz` archive. Two different `.itp` files are provided: one containing only one set of parameters (`caffeine_A.itp`), and one containing also parameters for a dummy atom state (`caffeine_AB.itp`). Remember to adapt the `.top` file to `include` the one you are using. Furthermore, a file containing octanol coordinates that can be used with the `genbox` command (`-cs` option) to produce starting coordinates for an octanol solution is given (`octabox.gro`).

What strategy are you using to calculate the change in solvation free energy?
What value do you get for the change in solvation free energy and for $\log P$?
How does that compare to literature?
Attach curves relevant for your calculation methods any other material necessary to understand, or illustrative for your calculations!