Notes on Computing Menthone Equilibrium Values

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A method for computing the equilibrium constant for the *cis*- and *trans*-menthone isomers (from the computed energy difference between the two diastereomers) is to determine the mole fraction of each component from a Boltzmann analysis of all of the important minimum energy conformations on the potential energy surface. The mole fractions for the subset of all conformations for the trans isomer and, separately, for the cis isomer can then be individually summed and those final two ratios compared to establish the computed equilibrium value from the free energy difference of the two states (i.e., the cis vs. the trans isomer).

The mole fraction of any *i*th component of a set of *n* species in equilibrium with one another can be expressed by the Boltzmann probability distribution. One representation of this is:

$$\text{mole fraction of the } i\text{th component of } n \text{ species in equilibrium} = \frac{\exp\left(\frac{-E_i}{RT}\right)}{\sum_{i=1}^{n} \exp\left(\frac{-E_i}{RT}\right)}$$

This information, even for large values of *n*, can be easily managed with an Excel spreadsheet. *It is instructive for you to create your own Excel worksheet from scratch*. I have posted on the course website PDFs of two "sheets," the second shows the formulae for each cell; the first shows the actual values. I constructed the Excel spreadsheet I used to make these PDFs using data that a past 2312 student had calculated for her Monte Carlo multi-conformation search of the two menthone isomers using chloroform solvation. While there were ~18 minima found for each isomer, I only entered the data for those (eleven, in total) conformations that were within 15 kj/mol (*i.e.*, ~3.6 kcal/mol) of the global minimum energy conformer. This cutoff value of 15 kj/mol was somewhat arbitrarily chosen, but it is safe to assume that any higher energy conformers will contribute such a small amount to the overall population that they can be readily ignored. At the bottom of the spreadsheet, I have also calculated the equilibrium constant (= 7.7) by only considering the lowest energy conformer (the so-called "global minimum") for the trans isomer (t-1; 24.6 kj/mol) with that of lowest energy conformer of the cis isomer (c-1; 30.3 kj/mol). Notice that I have calculated the data at 65 °C (338 K), which you can spot as T in the EXP(cellname/RT) terms. Notice also that considering the population contributions from the eleven conformers rather than just two makes an appreciable difference in the computed K_{eq} (*i.e.*, 7.7 vs. 5.2). Your exact numbers will differ from these because you will i) use water solvation (a better solvation model for methanol), ii) a different forcefield, and a T of 22 °C (295 K) because you will carry out the equilibration at ambient temperature).

Create a similar spreadsheet and enter the data that you obtain for the various conformations of the two isomers following your MacroModel conformational search. Compute your K_{eq} by analogy to what I have done here. *Please use the water solvation model* (the best approximation for the polar protic solvent methanol that you will use for the equilibration experiment) and the Merck-modified force field (MMFM) that you use in your computations when you report your computed K_{eq}. *Include a one-paragraph description/discussion describing and summarizing the results of your calculations and turn in your completed Excel worksheet as part of Report #2. Indicate the temperature you have used in your computation.*