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 conformer in each of the diastereomers 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 of mole fractions 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 in order to better appreciate the approach.* I have posted on the course website a PDF haviung two pages, each of a "sheet" from an Excel spreadsheet. The second page shows the formulae used for each cell; the first page shows the actual values. I constructed the Excel spreadsheet that I used to make this PDF using the energies that a past 2312 student had calculated using a Monte Carlo multi-conformation search (as implemented in a molecular mechanics program called MacroModel) of the two menthone isomers (i.e., trans- and cis-) 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 16 kj/mol (*i.e.*, ~4 kcal mol^{-1}) of the global minimum energy conformer. This cutoff value of 15 kj mol^{-1} 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^{-1}) with that of the 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 all eleven conformers rather than just two makes an appreciable difference in the computed K_{eq} (*i.e.*, 7.7 vs. 5.2).

The energy values you will use for your spreadsheet will differ from those in the PDF I have uploaded because they come from a set of density functional theory (DFT) computations that Jingyang has carried out. DFT gives more reliable energy values than the simpler molecular mechanics calculations that are used by MacroModel. He used methanol as a solvation model in the DFT computations and a T of 25 °C (298 K) because that is close to the temperature at which most of you carried out your equilibration of the menthone isomers.

Boltzmann Analysis of the trans- vs. cis-Menthone Equilibrium Ratio from DFT Energies

To see the structures of .pdb files (Protein Data Bank) in a folder I will provide, you can use Chem3D or Avogadro v.1.99. As a Mac user, I prefer the latter because it avoids the hassles of using Chem3D via Citrix at apps.umn.edu. Avogadro is also more robust in the things it can do. Avogadro is freely downloadable from:

https://two.avogadro.cc/install/index.html

I will also provide a folder of .png files, where you can see a static image of each of the conformers resulting from the DFT optimizations.

Create a similar spreadsheet modeled after the templates you can view in the PDF you can download from "Template (a 2 page PDF) for Creating Your Excel Spreadsheet for the Menthone Boltzmann Equilibrium Values (posted 11-14-24)" from our website. Use the energies of the optimized DFT structures that Jingyang calculated. They are found in "Excel file of the DFT energies for the conformations of the trans- and cis-menthones (posted 11-13-24)." **Note: The conformation #s in that file (#1-7 for the cis and #1-8 for the trans) are not ordered by their relative energies.**

Details for what I will ask you to turn in are not yet finalized from this point on. I will finish and send that to you soon. (Thursday, Nov. 14, 2024).

Compute the K_{eq} from the DFT energy values by analogy to what I have done in the model sheets in the PDF file.

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.