Chemistry 4021/8021 **Computational Chemistry** 3/4 Credits

Spring Semester 2009

(Due 2 / 23 / 09)

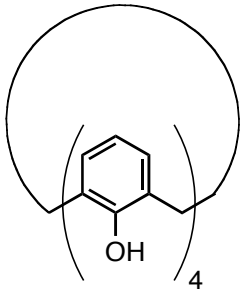
Answer Key

1. What are the parameters for the force constant (mdyne/Å) and equilibrium bond length (Å) for the bond between a carbonyl carbon and a carbonyl oxygen in each of the MM3, MMX, and MMFF94 force fields? What is the parameter for the equilibrium bond length between two sp^3 carbon atoms in the MMX force field? If you were to pick a "canonical" value for a C–C single bond between two sp^3 carbon atoms, what would it be to the nearest hundredth of an angstrom? How does that compare to the MMX parameter? Run a geometry optimization of ethane with the MMX force field. Is the optimized C–C bond length equal to the equilibrium bond length parameter? If not, explain why not.

C=O parameters: MM3, 10.1 mdyne/Å, 1.208 Å; MMX, 10.8 mdyne/Å, 1.208 Å; MMFF94, 12.95 mdyne/Å, 1.222 Å.

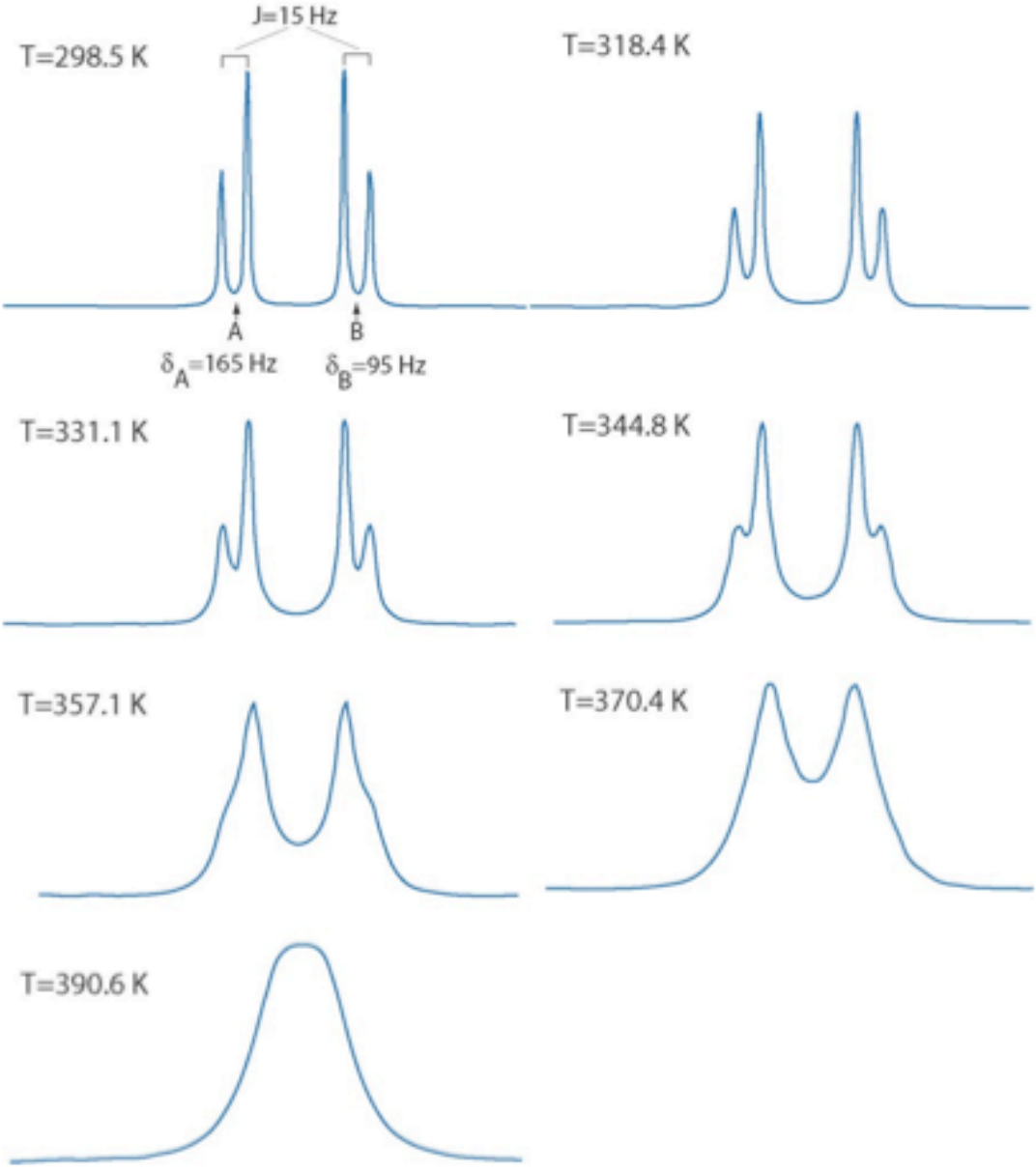
MMX C–C equilibrium bond length: 1.523 Å. The usual value in textbooks for a C–C single bond between two sp^3 carbon atoms is 1.54 Å, which is longer. However, the geometry optimization with MMX leads to a value of 1.532 Å. The reason it is longer than the parameter is that there are other strain contributors that must be minimized other than just bond stretch (primarily the repulsive non-bonded van der Waals interactions between the H atoms on the two different methyl groups, which contribute 0.679 kcal/mol worth to the total strain of 0.816 kcal/mol).

2. The structure of calix[4]arene (yes, there *is* a Wikipedia page on calixarenes…) is shown below.



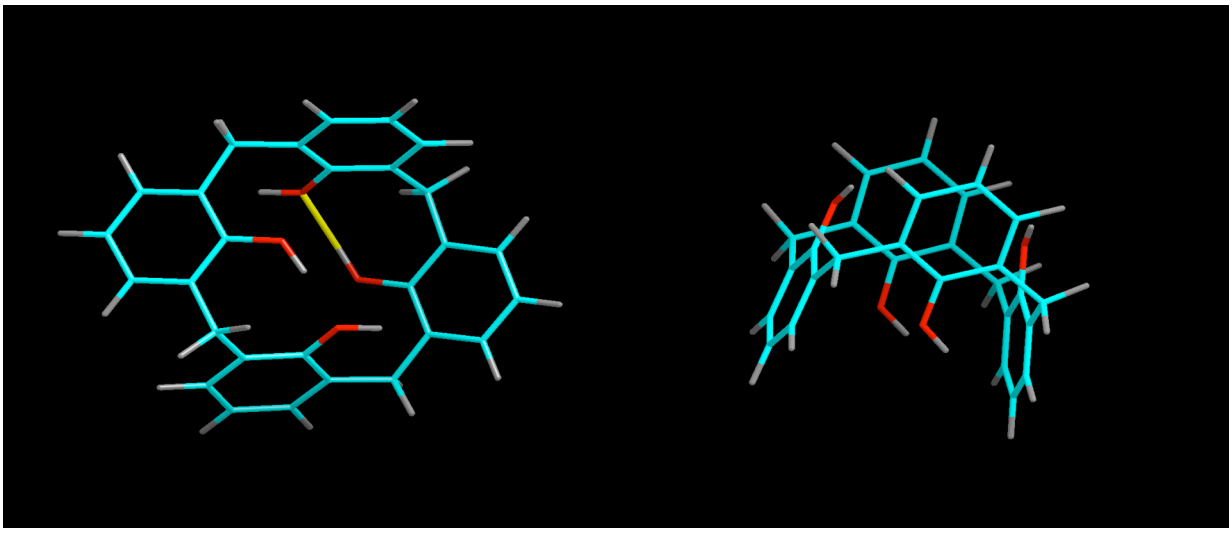
In $CDCl_3$, the ^1H NMR spectrum of calix[4]arene shows a clean doublet of doublets at about 4 ppm at room temperature that integrates to two-thirds of the number of aromatic protons. As the temperature is raised, the doublet of doublets

collapses to a singlet (see spectra on next page). Use PCModel and the MMX force field to rationalize this behavior. When two equivalents of ammonium perchlorate are added to the solution, the doublet of doublets remains largely unchanged even at 400 K. Why might this be?

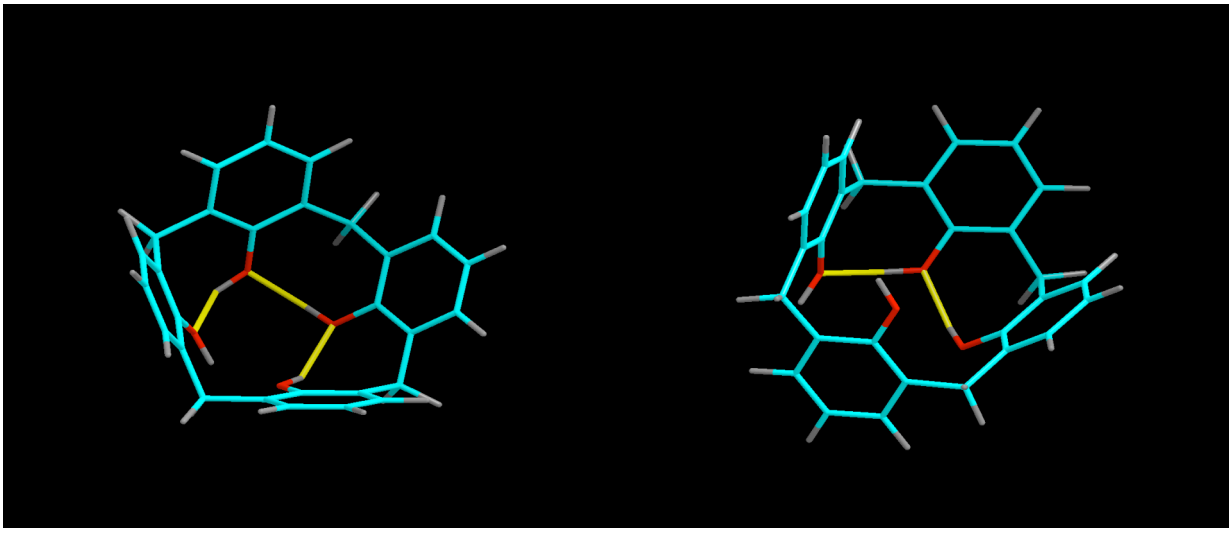


The spectra above illustrate the coalescence of an AB quartet. At high temperature both protons (which are from the bridging methylene groups) are chemically equivalent and isochronous, but at low temperature they

must be in different chemical environments that do not readily interconvert. This situation is consistent with a low-energy structure showing such a difference in environments that can isomerize to interchange the two protons at higher energies (so that higher temperatures speed the process relative to the NMR timescale).



22.5 **27.6**



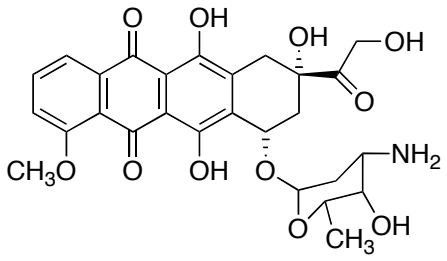
14.4 **22.0**

The four phenyl rings of the calixarene (calix means "chalice") can all be on one "side" of the molecule, forming a bowl-like cavity between them, and this permits the hydroxyl groups to hydrogen bond with one another. This structure (lower left, above) is predicted to be very stable compared to the 3 possible alternatives, where one ring is flipped (lower right,

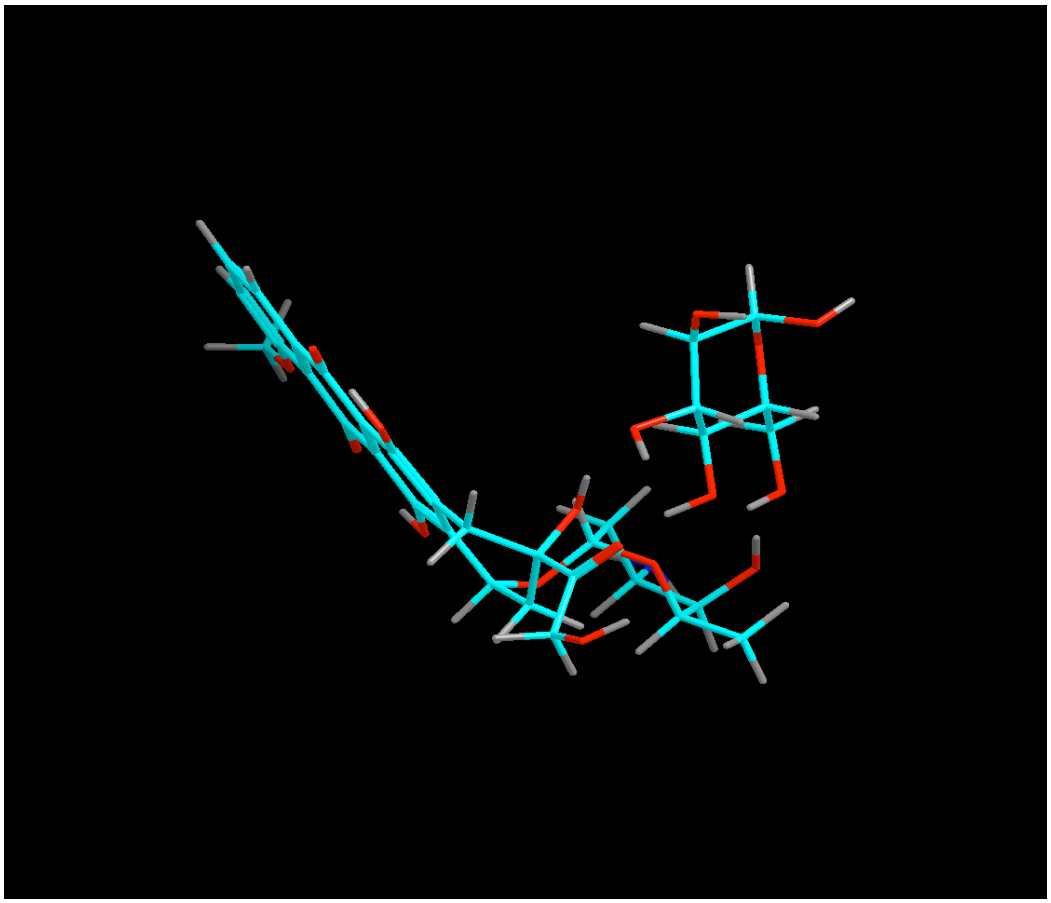
above), or two rings are flipped, in the latter instance 1,2 (upper left, above) or 1,3 (upper right, above) related to one another. The structures are shown together with their steric energies (kcal/mol) from MMX calculations with the hydrogen bonding option turned on. In the cone conformation, all 4 methylene groups are related by symmetry, but the two protons are in different environments, one pointing outwards from the chalice, and one downwards. However, by flipping the cone (going through the one-flipped conformation, to the lower-energy two-flipped conformation, back to a one-flipped conformation that is the mirror image of the first one, and from there to the mirror-image cone) the two hydrogen atoms are exchanged.

When ammonium perchlorate is added, the ammonium ion can nestle very comfortably in the calix, and ammonium ions are well known to interact strongly with the π clouds of aromatic molecules. This increases the barrier to ring flipping, since such a flip reduces the total interaction energy, so that in this experiment we do not reach a temperature sufficiently high to drive it.

3. Ripped from the research press! The Arriaga group in this Department (and in particular Joe Katzenmeyer) has found an unusually strong binding between the antibiotic doxorubicin (below) and glucose. This could have in important impact on the drug's distribution in the body or in cells and they would like to understand it better.



On the course website, in the Problem Set section, I have provided a PCModel file corresponding to one complex of doxorubicin and glucose that I have found. Go to the website, copy the text, and create a text file named startpoint.txt on the computer that you are using with PCModel (be sure to save as text only if you are using a word processor). Open the file with PCModel -- it should appear as below.



Choose the MMX force field and mark hydrogen bonding on. Minimize the molecule — you should get a steric energy of 35.15 kcal/mol. If you did, you are now ready to start! Find a lower energy structure by moving the glucose around, changing hydrogen bonds, etc. Note that it can be quite helpful to use the "SelAtom" button, click on one atom of the glucose, and then go to the Substr menu and select "Move". If you want to rotate/move both molecules later, you need to click SelAtom again first, or strange things may happen.

If/when you find a lower-energy structure, save it as a file so that you don't lose it (of course, you can save as many files as you like if you don't want to lose intermediate structures while you're working).

You may find that you want to use the GMMX utility to sample the conformational possibilities more completely. You will need to add the rings and rotatable bonds to the search criteria using the appropriate buttons in the GMMX dialog box. You might want to play with GMMX a bit in a simpler system to get a feel for what it does, and choose fewer than 100000 steps unless you want to wait a LOOOOOONNNNNNGGGGG time. If you DO use GMMX, turn OFF the pi

calculation option. Note that, at least on my Mac, GMMX has a quirk that turns off H bonding for its final steps, so you'll want to do a final reoptimization of any structures you locate this way with H-bonding turned back on.

Full credit for this problem consists of emailing me your *lowest-energy* structure in exactly the same format as the text file from which you started (so that I can run the molecule, too, and verify your steric energy, which you should send me when you send the file itself). Just to whet your competitive spirit, my lowest-energy find so far is 25.9 kcal/mol. Good luck!

The Arriaga group is grateful for the support.