*Using PC Model, answer the three questions below.*

1.   How many different carbon atomic types are there in each of the MM3, MMX, MMFF94, and Amber force fields? Which force field has the least number, and why do you think that is?

MM3: 24; MMX: 19; MMFF: 15; Amber: 13.

The small number for Amber is consistent with this force field being parameterized only for amino acids and nucleotides. The smaller range of chemical diversity limits the total number of carbon atom environments needing to be modeled.

2.   Chemical degradation studies indicate a recent fungal extract having anticancer properties to have the chemical structure indicated below. Using the MMX force field with default settings, find 3 distinct structures for this molecule (make sure you get the stereochemistry right!—the bold black dots in the structure represent H atoms coming toward you from the plane of the paper) Print the structures and record their energies. Prior to completing the rest of the problem, express your confidence level (on a scale from 0 to 100%) that you have found the global minimum energy structure.
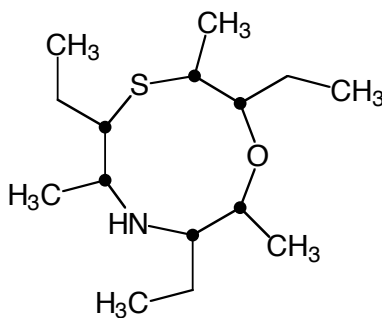
There are many, many possibilities for the first three structures, so they are not listed here. Confidence level is a matter of personal opinion, but should probably be low…

Now, use the GMMX utility to stochastically search for the global minimum. You will need to add the ring and rotatable bonds to the search criteria using the appropriate buttons in the GMMX dialog box. In addition, to save some time, open the Options dialog box and set the minimum number of optimizations to 100 and the maximum number to 200 (the bottom two boxes). It will take a few minutes for the process to complete once you have told it to begin.

Print the structure and report the MMX energy and all of its components (Str, Bnd, etc.) for the global minimum that was found. Which individual component contributes most to the strain? Does any component contribute in a favorable (i.e., negative) way? If so, what particular interaction seems to be involved? What is the predicted heat of formation? What is the predicted dipole moment? How do you think this was computed? What is the predicted XLogP? What is XLogP and how is it computed?
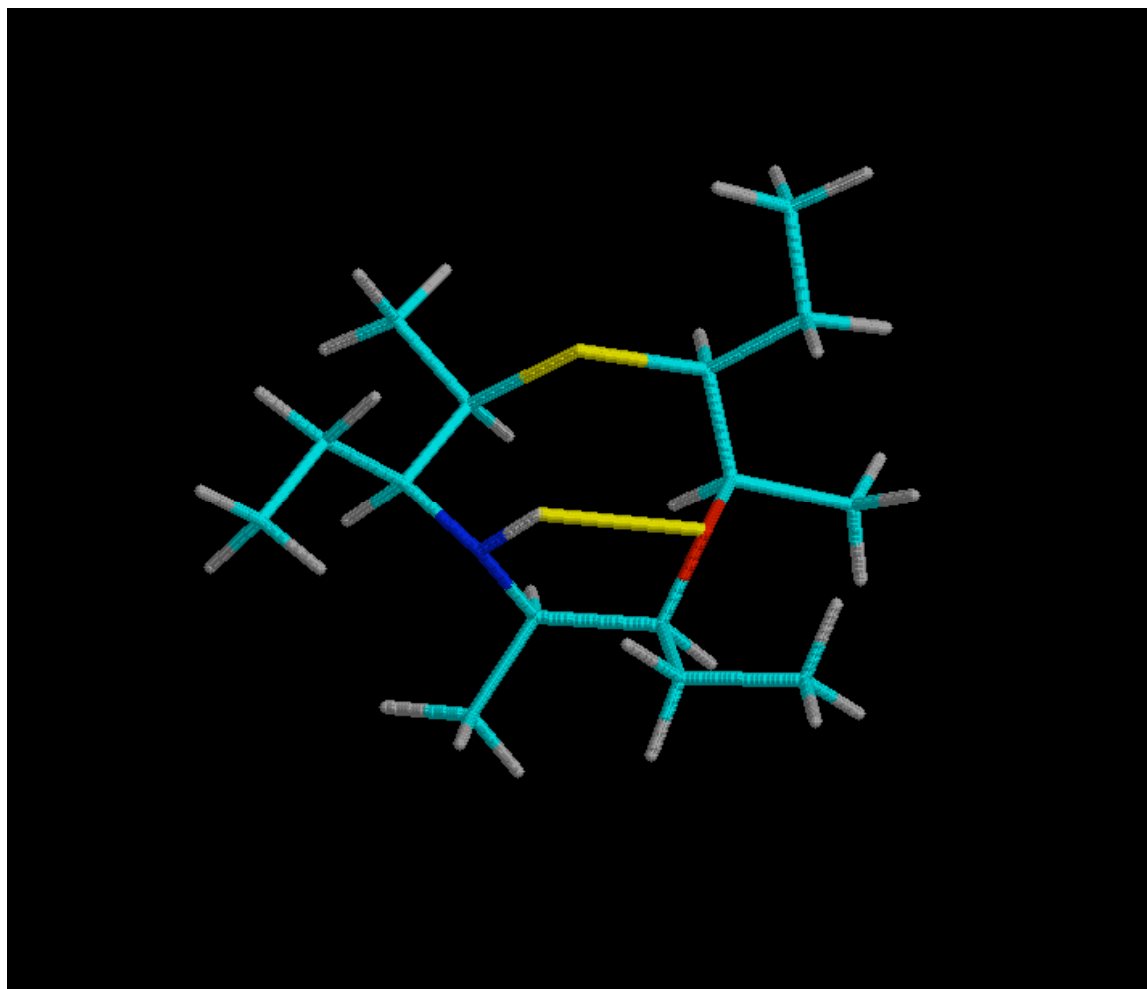
All units kcal mol^{-1}: MMXE = 23.210; Str=1.826; Bnd=6.804; OOP=0.000; StrBnd=0.793; Tor=10.127; VDW=8.449; QQ=-4.789

The largest contributor to strain is torsional strain. The charge-charge term is favorable, presumably because of the cross-ring hydrogen bond between the amine proton and the ether oxygen (indicated by a yellow line, not to be confused with the sulfur bonds, in the structure above).

The heat of formation is predicted to be −100.34 kcal mol^{-1}. The dipole moment is predicted to be 2.8 D. As the only charges present in the force field are the partial atomic charges used to compute the QQ interaction, presumably the force field computes the dipole moment as

$$\mu = \left| \sum_{i}^{\text{atoms}} q_i \mathbf{r}_i \right|$$

where q is the partial atomic charge from the force field and $\mathbf{r}$ is the atomic position. As long as the molecule is uncharged, the magnitude of the dipole moment is independent of the choice of origin, so we could express $\mathbf{r}$ as $x\mathbf{i} + y\mathbf{j} + z\mathbf{k}$ where x, y, and z are the cartesian coordinates of the atoms from the force field and $\mathbf{i}$, $\mathbf{j}$, and $\mathbf{k}$ are the cartesian unit vectors.

The predicted XLogP value is 3.339 log units. This is a predicted octanol/water partition coefficient that depends only on group contributions (i.e., it is the same irrespective of conformation). See http://www.compchemcons.com/xlogp/xlogp.html.

> Did your final structure match one of the three you found originally? Having finished this exercise, express your confidence level (on a scale from 0 to 100%) that you have found the global minimum energy structure. If not 100%, what else might you do to raise your confidence level?

There is never a guarantee of having found the global minimum in any search process, but the number of minima for this molecule is probably sufficiently small that our limited search may be considered to have about a 95% probability of having found the global minimum. To improve our confidence, we could (a) run the search longer, (b) explore results from other force fields (classical or quantum, although the latter would be frighteningly expensive) to ensure that the MMX force field is not

either poorly parameterized or missing some particular conformer, and/or (c) explore other search algorithms.

> Finally, of all of the structures found in your search, what percentage of the population does the global minimum comprise at 300 K? (You'll need to look for an output file to answer that question and open it with a text editor.)

From my .pkm output file:

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 GMMX Conformation Search Output Results
 Temperature for Boltzmann Calculations: 300.00
 Average Energy:    23.498 Kcal/mol
 Average Heat of Formation: -100.052 Kcal/mol
 Average Dipole Moment:    2.78
 Dipole Moment Squared:    7.72
Pop conf      1 =    34.11   E =    23.210 DE = 0.000 HF = -100.340
DHF = 0.000 DPM = 2.797
Pop conf      2 =    28.27   E =    23.322 DE = 0.112 HF = -100.228
DHF = 0.112 DPM = 2.791
Pop conf      3 =    22.28   E =    23.464 DE = 0.254 HF = -100.086
DHF = 0.254 DPM = 2.719
Pop conf      4 =     6.14   E =    24.233 DE = 1.023 HF =  -99.317
DHF = 1.023 DPM = 2.810
Pop conf      5 =     5.67   E =    24.280 DE = 1.070 HF =  -99.270
DHF = 1.070 DPM = 2.802
Pop conf      6 =     1.10   E =    25.257 DE = 2.047 HF =  -98.293
DHF = 2.047 DPM = 2.792
Pop conf      7 =     1.02   E =    25.304 DE = 2.094 HF =  -98.246
DHF = 2.094 DPM = 2.775
Pop conf      8 =     0.83   E =    25.428 DE = 2.218 HF =  -98.122
DHF = 2.218 DPM = 2.715
Pop conf      9 =     0.59   E =    25.626 DE = 2.416 HF =  -97.924
DHF = 2.416 DPM = 2.801

Entropy of mixing is:    3.10 cal/mol-K
At 300.00 deg K,    TdS =    0.93 Kcal/mol
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So, 34.11% evidently. However, one might want to visualize the other two low energy structures to verify that they truly distinct structures from the global minimum, since they vary in energy from it by only 0.11 to 0.25 kcal mol^{-1}.

3.   The unsaturated ketone below reacts with lithium dimethyl cuprate in two steps. In the first step, the nucleophilic methyl anion adds in a Michael fashion to the β position of the double bond. In the second step, the intermediate enolate anion is protonated by the work-up buffer solution to generate the final product. Gas chromatographic (GC) analysis indicates a single product, presumably

stereochemically pure. In the nuclear magnetic resonance (NMR) spectrum, the non-bridgehead proton that is α to the carbonyl group is readily apparent at 2.3 ppm. It appears as a doublet of quartets with the doublet coupling $^3J_{HH} = 5.3$ Hz. When this product compound is dissolved in methanol containing a trace of NaOMe, left overnight at room temperature, and re-isolated, GC indicates it to be a mixture of a small portion of the original product and one new substance. In the NMR, in addition to weak peaks corresponding to the original spectrum, there is now a doublet of quartets at 2.4 ppm with the doublet coupling $^3J_{HH} = 7.3$ Hz.
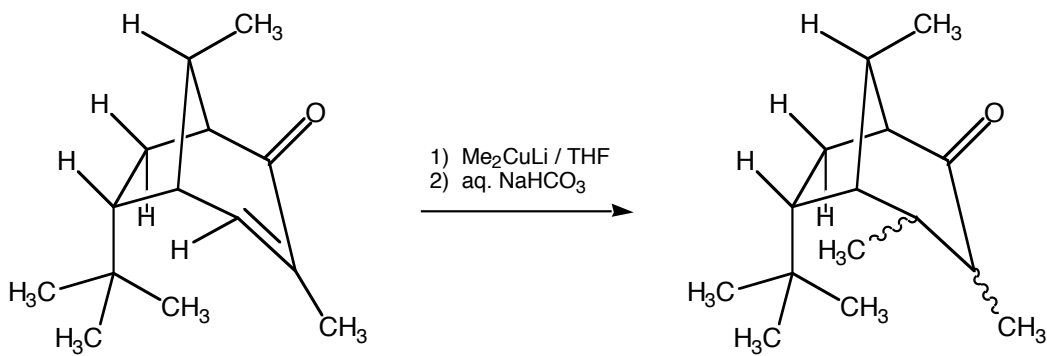
What is the integration ratio of the doublet of quartets at 2.3 ppm to that at 2.4 ppm at 298 K? Explain how you arrived at your answer using the MMFF force field; in your explanation, emphasize mechanistic analysis.

The integration ratio is very slightly more than 12:1 for 2.4 ppm vs. 2.3 ppm in the final spectrum.

One arrives at this conclusion from noting that there are four possible stereoisomers for the final product, (exo,exo), (exo,endo), (endo,exo), and (endo,endo), where the descriptors refer to the orientation of the methyl groups α and β to the carbonyl, respectively. The orientation of the β methyl group is set by the face from which the cuprate reagent reacts, while the orientation of the α methyl group derives from the face of the enolate anion that is protonated.

If we optimize all 4 structures with the MMFF force field and compute $^3J_{HH}$ values for the coupling between the protons at the α and β positions, we obtain (Hz): (exo,exo) = 7.1; (exo,endo) = 11.6; (endo,exo) = 5.4; and (endo,endo) = 8.5.

The experimental results are most consistent, then, with the first structure being the (endo,exo) stereoisomer and the second structure being the

(exo,exo) stereoisomer. Mechanistically, this is consistent with the cuprate addition taking place stereospecifically from the exo face and the bicarbonate protonation step also taking place stereospecifically from the exo face, thereby generating the (endo,exo) stereoisomer:

However, the subsequent dissolution in MeOH with a trace of base permits thermodynamic equilibration of the α position given the acidity of the enolizable proton. If deprotonation/reprotonation occurs with inversion of configuration, the (exo,exo) stereoisomer is generated:

MMFF predicts the force-field energies of the two isomers above to be 65.46 and 63.98 kcal mol^{-1}, respectively. If we assume ΔG is equal to force field ΔE we can compute the equilibrium constant K between the two as

$$K = e^{-\Delta E / RT}$$

where R is the universal gas constant and T is the temperature. At 298 K, we thus predict an equilibrium constant of 12.2.

As the initial product formed is not the most stable one possible, it is evident that bicarbonate protonation occurs with kinetic control, and the pH of the buffer solution is insufficient to permit the enolate center to epimerize.