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

Spring Semester 2010

(Due 2 / 22 / 10)

Using PC Model, answer the questions below.

1. In the AMBER and MMFF94 force fields, what are the parameters for the force constants and equilibrium bond lengths for the bond between an alkyl carbon and an amine nitrogen? How closely do the two force constants agree?

In the AMBER force field, an alkyl carbon is atom type 1 and an sp^3 nitrogen is atom type 20. The relevant stretch line from the parameter file is

bond 1 20 367.0 1.4710

In the MMFF94 force field, an alkyl carbon is atom type 1 and an amine nitrogen is atom type 8. The relevant bond stretch line from the parameter file is

bond 1 8 5.0840 1.4510 C94

Quick reference to the PC Model manual suggests that the equilibrium bond lengths are 1.471 and 1.451 in units of Å for AMBER and MMFF, respectively. The force constants clearly are *not* in the same units. Referring again to the manual, it appears that the units for AMBER are (367.0) kcal/mol-Å^2 and the units for MMFF94 are (5.084) mdyne/Å. To convert from mdyne/Å to kcal/mol-Å^2 involves a factor of 143.84 kcal/mdyne-mol-Å, which renders the MMFF94 constant 731.3 kcal/mol-Å^2. At first glance, this seems surprising. How could two different force fields disagree by so large a margin? However, some studying of the parameter files indicates that the factor of ½ that appears in the "usual" force field expression for a harmonic term is included already in the 367.0 value used by AMBER, but not in the MMFF94 case, so that the AMBER force constant is really 734.0 kcal/mol-Å^2, or within 0.3% of the MMFF94 value (the sort of close agreement one expects given the well characterized nature of this bond).

Optimize methyl amine using the AMBER force field. What is the C–N bond distance and what is the bond stretching strain? Now, fix the C–N bond to a *different* bond length and compute the bond stretching strain. Is it equal to the expected value? Explain how you carry out this calculation and how you compute the "expected value".

Optimized methyl amine with AMBER has a C–N distance of 1.471 Å and a bond stretching strain of 0.000; the structure adopts the equilibrium bond length and has no strain. By selecting the C and N atoms and then selecting Mark/Fix Distance, with a fixed distance of 1.6 Å and a force constant of 1000, and then performing a minimization, one can get a structure having a C–N bond length of 1.565 Å. Deleting the fixed distance and doing a single point energy calculation gives a stretching strain of 3.267 kcal/mol. If we evaluate 367 kcal/mol-Å^2 x (1.565 Å – 1.471 Å)^2 we compute 3.243 kcal/mol, which is almost perfect agreement (the difference arises from very small changes in other force field terms).

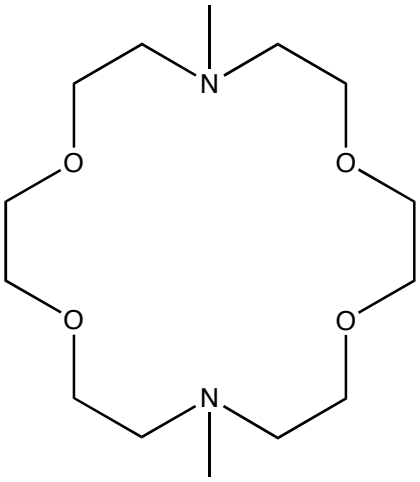
> Stretch the C–N bond by the same amount with MMFF94. Is the increase in bond stretch strain for MMFF94 consistent with the AMBER value and the relative force constants for the two force fields? If not, why not?

In my case, I need to stretch the C–N bond from 1.451 Å (the equilibrium length in MMFF94) to 1.546 Å. The same procedure as that outlined above gives a stretching strain increase of 2.729 kcal/mol, which is only about 84% of the AMBER value. This is not consistent with the harmonic force constants for the two force fields being within 3% of one another. However, MMFF94 is *not* a harmonic force field: it includes cubic and quartic stretching terms to improve the shape of the stretching potential. As bonds dissociate as they are stretched, harmonic force fields (like AMBER) inevitably overestimate the cost of bond stretching, as we see here.

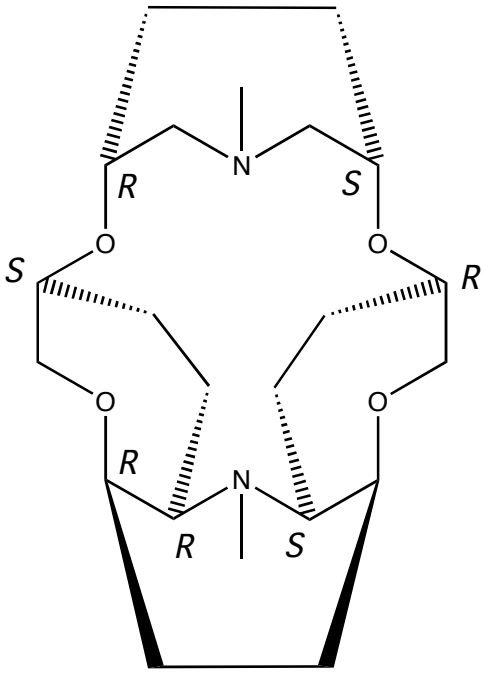
2. Oh no! Someone spilled a solution of plutonium salt onto the Chemistry Department's softball trophy from that famous 1934 championship that saw Mathematics and Chemistry go 73 scoreless innings over the course of four days before I. M. Kolthoff himself powered one over the left field fence, shattering the windshield of the Dean's Cadillac V16 Aerodynamic Coupe.

   You probably know that plutonium (Pu) is one of the deadliest substances on Earth in addition to being highly radioactive. But, we can't throw away the trophy! The only remedy will be to soak the wooden base, into which the Pu has leached, in a solution containing a sequestering agent that will extract the Pu from the wood until the remaining concentration of Pu in the wooden base falls below femtogram levels. The organic and inorganic chemists have huddled together, and propose the 3 molecules shown on the next page, each of which can be synthesized for the indicated cost per gram. Given that this money has to come out of the seminar donut fund, they want to choose the most cost effective option.

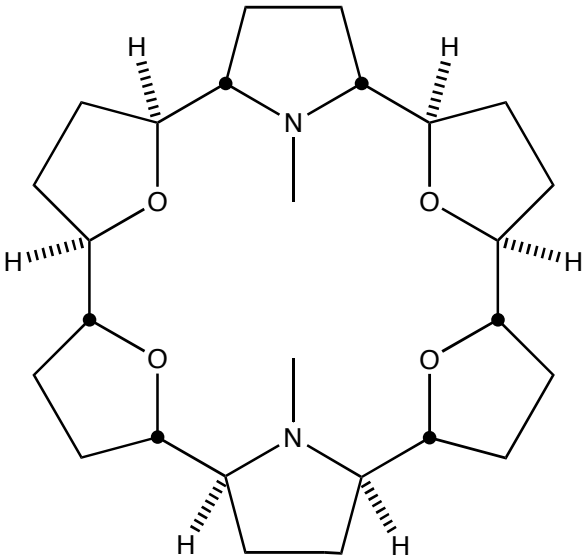
Which molecule should they make? Justify your answer on the basis of molecular mechanics calculations, explaining precisely and in detail what you did in order to come to some conclusion. (As it is mildly tricky to interpret stereochemistry for the final structure, absolute assignments at each position are provided for completeness.) For purposes of this exercise, let's assume the speciation of Pu is entirely high-spin Pu(IV).



$1.00



$1000.00



$10.00

This is by no means a trivial problem — many reasonable answers could be offered. Here's what I did:

First, the issue of synthetic cost is balanced by binding efficiency. If the third macrocycle costs 100 times the second, but binds 10,000 times stronger, it will be more cost effective to synthesize the more expensive one because it will require much less of it to leach the Pu to an acceptable level. Put more chemically, we care about the equilibrium

$$\text{trophy} \bullet \text{Pu} + \text{macrocycle} \Leftrightarrow \text{trophy} + \text{macrocycle}\bullet\text{Pu}$$

which has an associated equilibrium constant

$$K = \frac{[\text{trophy}][\text{macrocycle}\bullet\text{Pu}]}{[\text{trophy}\bullet\text{Pu}][\text{macrocycle}]}$$

where we want the ratio of trophy to trophy•Pu to exceed 10^{15}, which means we will want to maximize the binding of Pu to macrocycle. We can see this by expressing the above equilibrium as the sum of two others, namely

$$\text{trophy} \bullet \text{Pu} \Leftrightarrow \text{trophy} + \text{Pu}$$
$$\text{Pu} + \text{macrocycle} \Leftrightarrow \text{macrocycle}\bullet\text{Pu}$$

the first is a constant about which we can do nothing, but the second is what we have some hope of adjusting. So, how can we compute the free energy of binding? In practice, that's a lot of work, because free energy will require a careful sampling over phase space. But, a quick estimate can be had from replacing free energy with potential energy, and further assuming that we can deal just with lowest energy isomers. And, we can recognize that we aren't trying to get an accurate *absolute* binding energy, we just want a *relative* binding energy.

So, what controls binding energy? Well, let's assume that all 3 crowns will complex the Pu atom equally well once they adopt a nice geometry (see figure on next page for the second crown), so then the question becomes, how much energy must they lose in order to *adopt* that optimal structure compared to their lowest energy *uncomplexed* structure?

To estimate that, I chose the MMX force field. I generated the best structure I could for the simplest crown with a metal, Pu, chosen to be *bonded* (not metal coordinated) to the six heteroatoms. I chose bonded because the choice of

"metal coordination" led to only 4 heteroatoms being less than 3 Å from the metal, and I did not consider this reasonable. I might be making a mistake, but, hey, the trophy is glowing and I needed to make some progress, so there's no point sitting around existentially paralyzed about the whole thing.

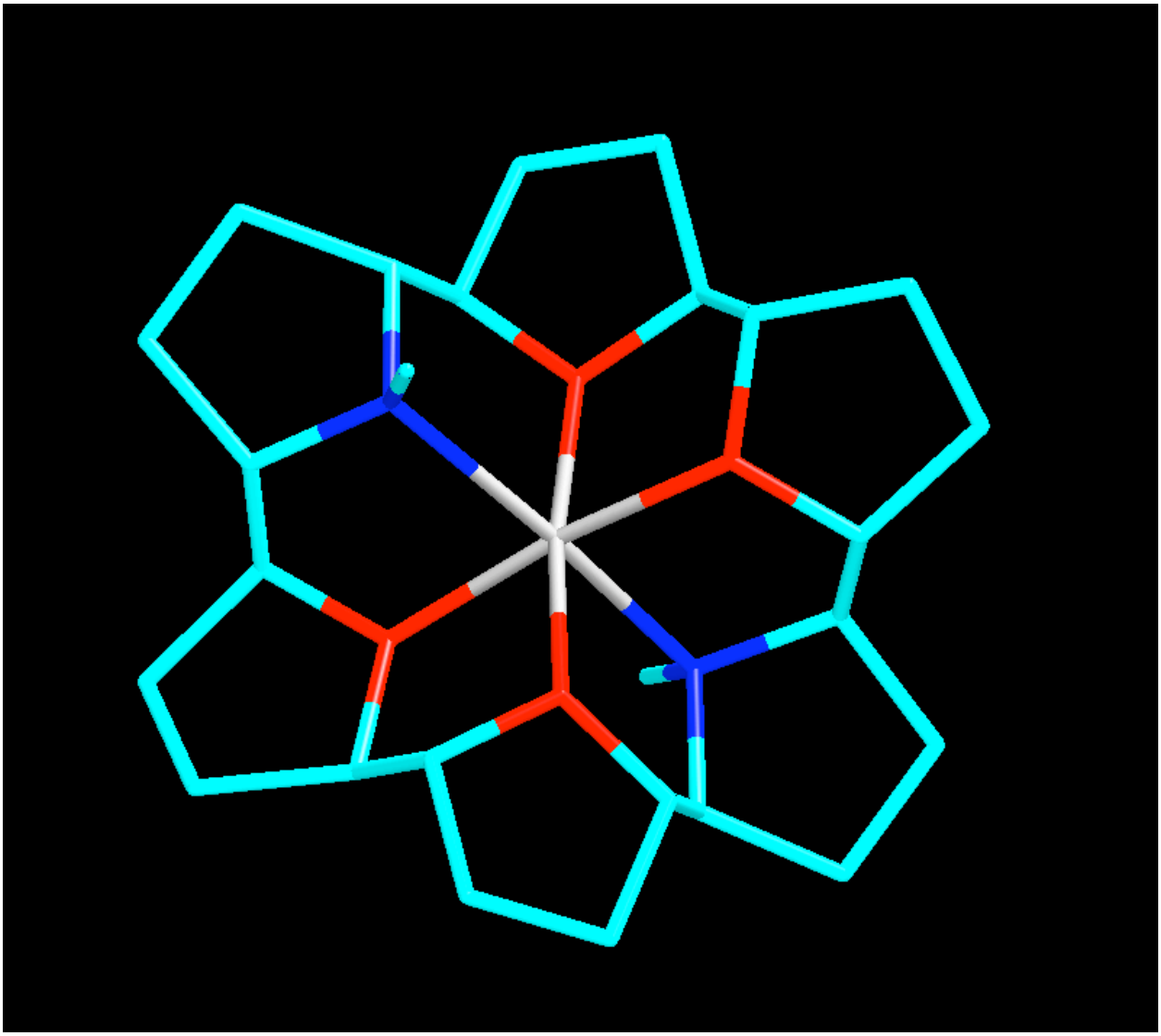


Figure. Tube representation of optimal crown•Pu complex for second macrocycle; hydrogen atoms have been removed for clarity. Carbon, nitrogen, oxygen, and plutonium atoms are cyan, blue, red, and gray, respectively.

Based on this geometry, I then generated analogous geometries for the other two crowns. In each case, I then deleted the Pu atom and computed single point energies for the crowns. Then, I minimized them and looked at how much the energy dropped; that is, what did it cost them to adopt that geometry. To be

thorough, I then did GMMX searches for the *global* minimum, taking 1000 steps in each case. As a technical point, I did all of this *without* lone pairs in the MMX calculations. However, for two cases, I checked whether including lone pairs made a difference, and they did not seem to affect my energy differences, so this point may have been moot. My results are shown in a table on the next page.

Table. Steric energies (kcal/mol) for different crowns.

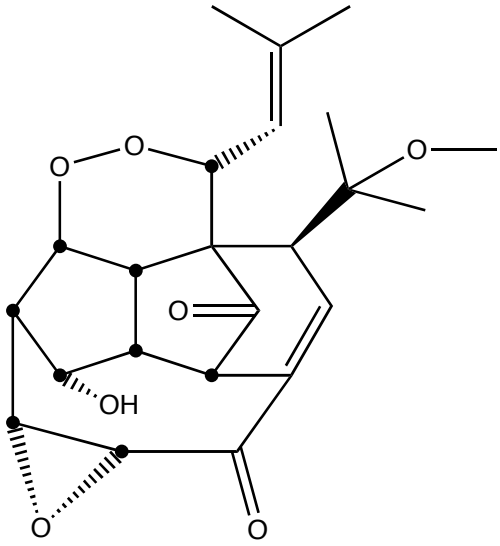
Cost ($)	Frozen[a]	Relaxed[b]	Fully relaxed[c]	Distortion cost[d]
1	85.6	44.4	35.0	50.6
10	123.0	95.1	89.2	33.8
1,000	135.6	104.3	97.1	38.5

[a] Computed for empty crown at the frozen geometry of the optimized crown•Pu complex. [b] Energy for structure that derives from direct geometry optimization of the frozen, uncomplexed crown. [c] Lowest energy structure found from 1,000 steps of GMMX optimization. [d] Computed as difference between columns 2 and 4.

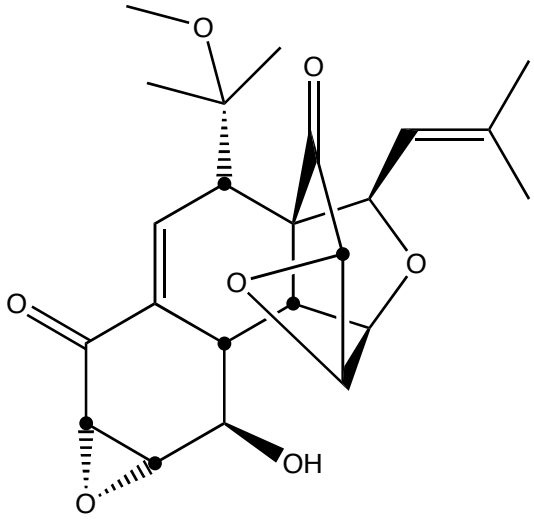
As can be seen from the table, the $10 crown has the lowest distortion cost to form the proper pocket to complex Pu. As that cost is much more than 1.4 kcal/mol better than that for the $1 crown, the improved binding is much better than the factor of 10 difference in the cost. So, the chemists should synthesize the $10 crown.

There are many other things that could be discussed with respect to this problem, and there are certainly other reasonable approaches that could be taken -- credit will be awarded based on logical thoughts/procedures, not based on absolute similarity to the solution proposed here.

3. We will use the MMX force field for this problem.



A



B

If your last name begins with any letter A through M, you are responsible for the structure on the left, **A**. If your last name begins with any letter N through Z, you are responsible for the structure on the right, **B**. Your responsibility is to find the two lowest energy structures that you can for your molecule. As you work, 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 decide that you want to use the GMMX utility to sample the conformational possibilities more completely. You will need to add rings and/or 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 100,000 steps unless you want to wait a LOOOOOONNNNNNGGGGG time. If you DO use GMMX, look carefully at your final structures to ensure that no stereochemistry was changed during the stochastic search process—it *can* happen.

For structure **A**, I found 3 structures, having steric energies of 94.99, 96.60, and 96.89 kcal/mol. For structure **B**, there are many more low energy structures: I found steric energies of 32.63, 32.77, 32.78, 33.61, 33.76, 33.83, 34.00, 34.09, 34.50, and 34.62 within the first 2 kcal/mol.