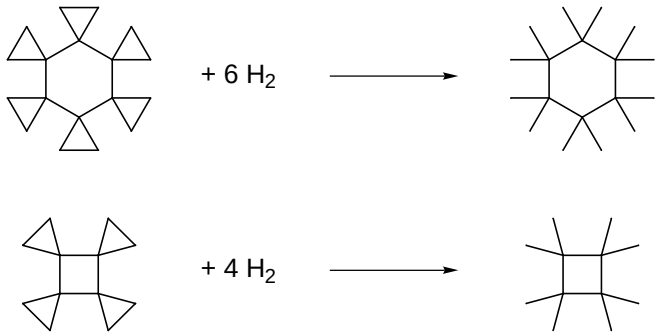
Chemistry 5021/8021 **Computational Chemistry** 3/4 Credits

Spring Semester 2003

(Due 2 / 24 / 03)

Using PC Model, answer the three questions below.

1. Using the MMX force field, compute the 298 K enthalpies of reaction for the two reactions below:



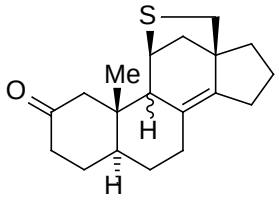
What is the enthalpy change per cyclopropane unit in each case? Examine the term-by-term change in each case and provide a physical explanation for the difference in the per-cyclopropane-bond change in the two molecules.

Molecule	Hexacyclopropyl cyclohexane	Dodecamethyl-cyclohexane	Tetracyclopropyl cyclobutane	Octamethyl-cyclobutane
Hf	136.87	-50.28	96.27	-50.11
MMX	61.939	85.130	45.513	36.506
Str	4.436	15.621	0.157	2.695
Bnd	18.353	18.559	21.471	19.706
OOP	0	0	0	0
StrBnd	-3.609	1.992	-0.146	0.239
Tor	41.930	14.211	27.072	7.071
VdW	9,828	34.746	-3.040	6.795
QQ	0	0	0	0

ΔH =	-187.15 Kcal/mol	-146.38 Kcal/mol
ΔH/cyclopropyl unit =	-31.19 Kcal/mol	-36.59 Kcal/mol

Upon examining the individual force field terms, the biggest difference between the two systems can be found in the van der Waals term, which differs by 15 kcal. The cyclohexane product contains much more steric hindrance due to trans-diaxial strain of the methyl groups. The cyclobutane system can avoid this strain by simply becoming more planar. Thus, the cyclobutane product is more stable, which gives rise to a greater enthalpy change per-cyclopropane-bond.

2. You have made the steroid derivative shown below, but are not certain of the stereochemistry of the indicated ring-junction proton. Happily, this proton is readily seen in the NMR spectrum, since it is allylic and coupled to only a single other proton. The doublet coupling constant is 4 Hz. Which isomer did you make? Explain how you arrived at your answer.



If you had carried out the reaction under thermodynamic conditions (i.e., conditions that would give an equilibrium distribution of the two epimers) what ratio of the two products would you expect at 298 K based on MMX, MM3, and MMFF calculations (show your computations, please)? What assumption(s) did you use in arriving at these answers? Finally, for one of these force fields, switch from using a charge-charge electrostatic term to a bond-dipole/bond-dipole term. How would your answer change vis a vis the equilibrium distribution? What if you maintain a charge-charge term, but change the dielectric constant to 4.0?

For simplification, we will refer to the isomer where the proton is *cis* to the methyl group as the *cis* isomer, and the one that has the proton *trans* to the methyl group as the *trans* isomer. The *cis* isomer gives a coupling constant of 0.65 Hz, while the *trans* isomer gives one of 3.50 Hz. Thus, you made the *trans* isomer.

Using the formula: $F(A) = [\exp(-\Delta G_A/RT)]/[\Sigma \exp(-\Delta G/RT)]$

we can use the heat of formation in place the free energy of formation. This assumes that the entropy of formation for each isomer is identical, which is a reasonable assumption since the molecules are so similar.

Force Field	*Trans*		*Cis*	
	Heat of Formation	% of product	Heat of Formation	% of product
MMX	-43.62	96.36	-41.68	3.64
MM3	-51.60	100.00	-44.05	0.00
MMFF94	-49.92	100.00	-42.15	0.00
DP_DP MMX	-43.62	96.36	-41.07	3.64
DP_DP MM3	-51.60	100.00	-44.05	0.00
DP_DP MMFF94	-49.92	100.00	-42.15	0.00
ε=4.0 MMX	-43.68	98.80	-41.07	1.20
ε=4.0 MM3	-56.73	100.00	-49.32	0.00
ε=4.0 MMFF94	-49.92	100.00	-42.15	0.00

3. Polyalanine is well known to form α helices in aqueous solution, while polyglycine has less of a tendency to do so. Construct α-helical structures of $(Ala)_6$ and $(Gly)_6$, end-capped with *N*-acetyl and MeNH groups at the N and C termini, respectively (don't try to cap the ends until you've already fully built the structure). With mark H-bonds turned on, minimize these structures. Evaluate your final structures with some care to ensure the optimization proceeded to give a reasonable α helix. Now, do the same thing, but for β sheet structures of both hexamers. Are the computed energy differences between α helix and β sheet for the two cases consistent with the experimental observation noted above? Examining the term-by-term contributions to the MMX energies, what is different about Ala and Gly (i.e., what causes the computed difference)? Provide a chemical interpretation of this difference and justify that interpretation. An experiment that may help you in your thinking is to try to optimize a β sheet structure for $(Val)_6$. Finally, how do the computed dipole moments for the α helices and the β sheets compare? What is the importance of any difference?

	(Alanine)6		(Glycine)6		(Valine)6
Measurement	α-helix	β-sheet	α-helix	β-sheet	β-sheet
MMX	-35.5	-23.5	-40.6	-32.5	-15.5
Str	1.0	1.11	0.47	0.42	2.64
Bnd	2.3	2.16	1.84	1.08	5.54
OOP	0.13	0.064	0.13	0.050	0.075
StrBnd	0.20	0.089	0.11	0.055	0.56
Tor	4.94	5.61	0.34	0.40	6.76
VdW	-3.28	8.39	-2.98	6.47	9.06
QQ	-40.8	-40.91	-40.53	-40.96	-40.15
Hf	-398.9	-386.84	-350.45	-348.29	-464.4
Dip	21.8	10.23	20.13	10.32	5.98

We see a difference in enthalpies of formation of 12 kcal/mol for the alanine hexamer but only 2 kcal/mol for the glycine hexamer. Thus, the computed results are consistent with the experimental results.

This difference is caused by an unfavorable steric interaction which can partly be seen in the VdW and QQ terms. The β-sheet hexamer of valine distorts to a washboard structure to avoid the poor steric interaction of alternating bulky groups. The α-helix structure spreads these bulky side chains away from each other much better. The two structures are not so different for glycine because the side chain of glycine is merely a hydrogen, the antithesis of a bulky substituent.

The α-helices have a much greater dipole moment than the β-sheets. Thus, in aqueous solution, this secondary structure is stabilized significantly.