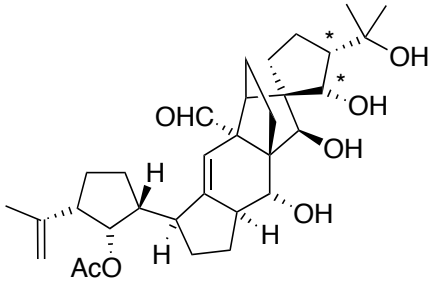
Chemistry 4021/8021 **Computational Chemistry** 3/4 Credits

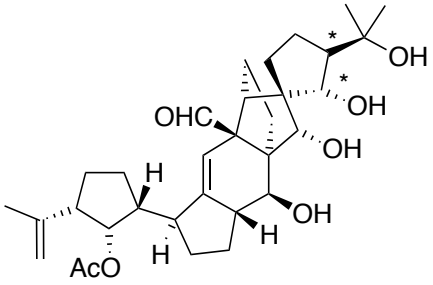
Spring Semester 2013

Answer Key

1. Let's return to our favorite natural products from the first problem set. In the templates subdirectory of my cm8021pr account, you will find two files, A_isomer.pcm and B_isomer.pcm, which contain the lowest energy structures that I found from my GMMX searches for these two structures. Convert these files to Gaussian input format and optimize the structures at the M06-L level of theory using the 6-31G(d,p) basis set together with an auxiliary density fitting basis set. In addition, specify an ultrafine integration grid. If you look at the file tmsopt.com in my templates subdirectory, you will see what keywords it takes to accomplish that.



A



B

Once your structures are optimized, report their absolute energies. In kcal/mol, which is more stable and by how much compared to the other? If they were interconverting isomers (which they most certainly are not, but *if* they were) what percentage would each contribute to a total population at 298 K? How does the DFT value compare to those computed from steric energies at the MMX, MM3, and MMFF levels in PCModel, when reoptimizing the provided structures?

Level of Theory	E_A, E_h	E_B, E_h	ΔE_{B-A}, kcal/mol	%A at 298 K
M06-L/6-31G(d,p)	-1773.516 76	-1773.474 04	26.8	~100%
Level of Theory	E_A, kcal/mol	E_B, kcal/mol	ΔE_{B-A}, kcal/mol	%A at 298 K
MMX	78.4	89.0	20.6	~100%
MM3	124.9	144.5	19.6	~100%
MMFF	161.9	178.6	16.7	~100%

The percentage is computed from eq. 10.49 of the textbook, but in this case the energy difference is so large in every case that we may as well say is preferred 100%.

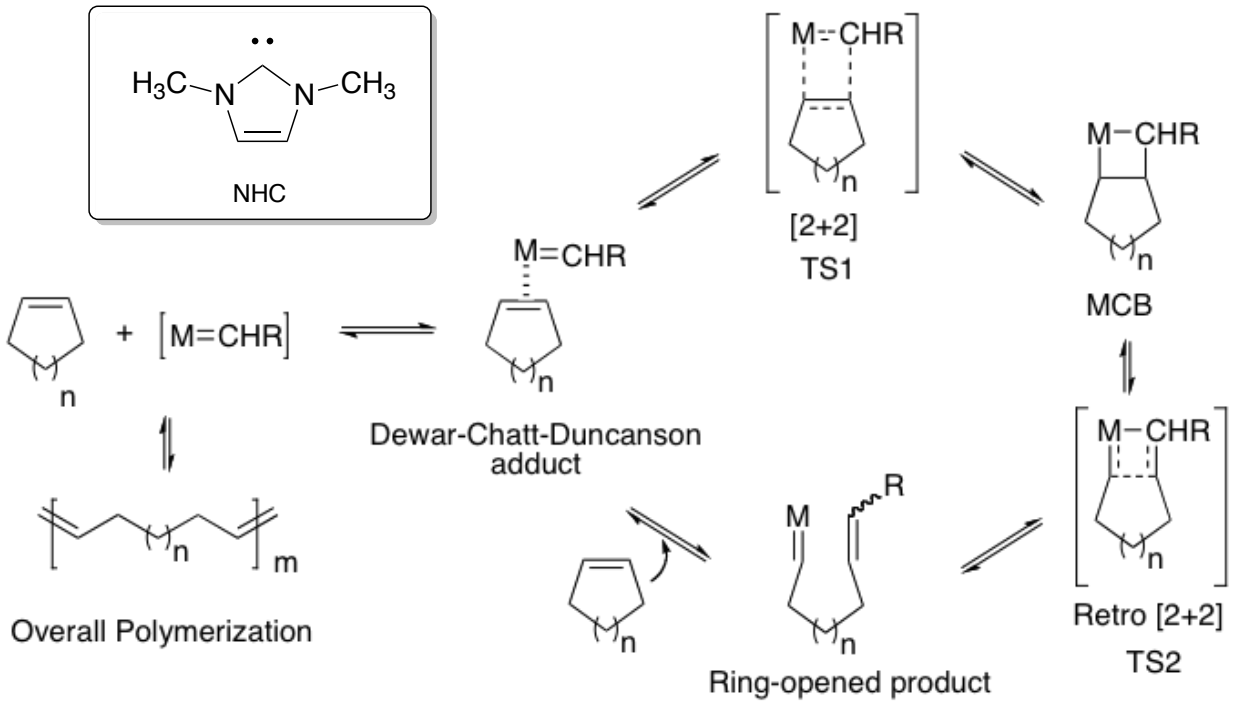
Now, compute ^{13}C NMR chemical shifts for both isomers as a single-point calculation on your optimized geometries at the M06-2X/6-31+G(d,p) level, i.e., ***do not reoptimize at this level***. The experimental data for the natural product are 201.9, 172.1, 157.4, 144.8, 114.8, 111.4, 78.1, 76.9, 75.7, 72.2, 71.2, 68.8, 62.5, 58.6, 57.9, 52.7, 52.1, 51.4, 50.7, 45.2, 39.0, 33.7, 31.0, 29.9, 29.4, 29.0, 26.6, 24.5, 24.4, 24.0, 23.2, 21.0 ppm relative to TMS. Which of **A** or **B** is the natural product? Explain how you came to your conclusion.

^{13}C expt, ppm	^{13}C A, ppm	^{13}C B, ppm
201.9	213.2175	216.1388
172.1	182.4242	177.0257
157.4	181.5424	168.9747
144.8	159.3507	157.8855
114.8	126.8978	133.3721
111.4	124.7054	130.1764
78.1	80.3283	83.8958
76.9	79.8647	81.4101
75.7	79.6901	78.6726
72.2	79.6587	74.9053
71.2	75.2245	73.0555
68.8	71.1326	71.6857
62.5	59.5363	62.9495
58.6	59.2432	58.9295
57.9	55.7728	58.7276
52.7	54.6607	57.937
52.1	54.6137	56.5318
51.4	52.9226	56.2125
50.7	52.8408	48.5397
45.2	52.6651	45.9181
39	40.0727	36.8351
33.7	36.66	35.9597
31	33.4087	33.8593
29.9	32.9021	33.8081
29.4	31.2356	31.198
29	30.9832	30.9062
26.6	29.5124	28.509
24.5	29.4856	27.5676
24.4	25.2864	27.2589
24	23.9101	25.253
23.2	23.5994	22.7591
21	22.8573	22.7258

One approach is to compare the experimental shifts to the computed shieldings (taken relative to the TMS ^{13}C shielding of 197.4 ppm provided in my templates file). That leads to the above table, where the shifts are simply ordered from highest to lowest:

Taking the root mean square error for computed A or B vs. expt gives values of 40.2 and 38.1 ppm, respectively, which seems to argue for B, but the difference does not inspire a lot of confidence. Maybe we could do better with a different calculation.

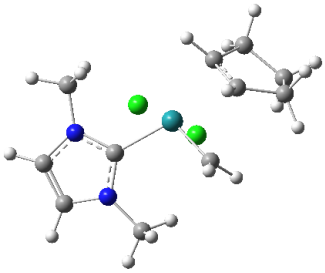
2. In ring-opening metathesis polymerization, a metal-carbene undergoes a [2+2] cycloaddition with a cycloalkene to form a metallacyclobutane-containing bicyclic intermediate. Subsequently, a retro-[2+2] reaction (that breaks the 4-membered ring in the opposite manner as its formation) leads to lengthening of the growing polymer and a new, reactive metal carbene. The process is illustrated below in general.



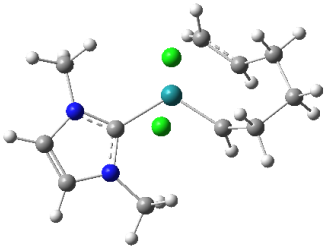
Your task is to characterize all 5 stationary points (the initial adduct, the intermediate, the final product, and the two transition-state structures; note that the final product has the terminal olefin coordinated to the metal) at a variety of levels for M = $Ru^{II}(NHC)Cl_2$ where NHC is the N-heterocyclic carbene shown in the inset to the figure above. The reaction is between $M=CH_2$ and cyclopentene (so, just as a check, all of your molecular formulas should be $C_{11}H_{18}N_2Cl_2Ru$).

Taking the initial adduct as the zero of energy, report the relative energies, enthalpies, and free energies along the reaction coordinate at the PM6 level. Then, repeat the process with full optimization and frequency calculations at the ωB97X-D/SDD|6-31G(d) level of theory. Finally, do *single point* calculations on the ωB97X-D structures at the MP2/SDD|6-311+G(2df,p) level of theory and report the HF and MP2 relative *energies* at that level of theory as well.

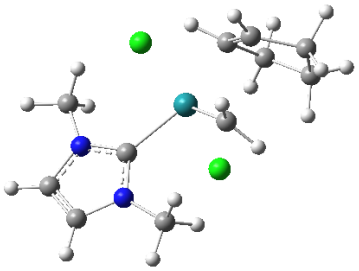
Here are pictures of the relevant structures (optimized at the ωB97X-D/SDD|6-31G(d) level.



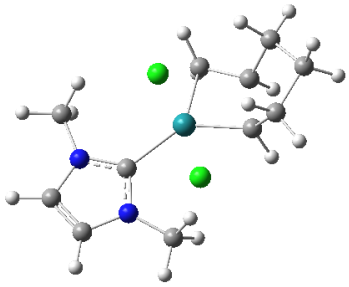
TS-1



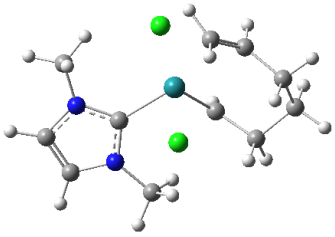
TS-2



Adduct



Int



Product

The first TS comes very quickly after the Adduct (as is also seen in the energy profile below), making it mildly challenging to find at the DFT level (and it does not exist at the HF or MP2 levels). In the Intermediate, the newly formed C–C bond is long enough (owing to strain) not to be recognized by Gaussview (so there is no bond drawn for the structure, but that is, of course, a completely arbitrary choice on the part of the graphics engine, *not* any kind of electronic structure information!) TS2 opens all the rings and leads to the final product that has a coordinated double bond (as does the adduct), ready for the next round of ring-opening polymerization.

The PM6 structures are not shown here, but they are in some instances rather different. They weren't very useful for pre-optimization.

Foregoing pretty formatting in the interests of time, here are the raw and relative energies, enthalpies, and free energies (E_h for absolute and kcal/mol for relative):

E

Level of theory	adduct	TS1	Int	TS2	Product
PM6	0.037 95	0.053 36	0.010 45	0.032 94	0.018 93
ωB97X-D	-1554.650 75	-1554.650 15	-1554.674 14	-1554.669 64	-1554.671 35
HF	-1549.179 26	-1549.173 69	-1549.182 52	-1549.189 73	-1549.198 87
MP2	-1551.986 05	-1551.989 24	-1552.018 13	-1552.009 65	-1552.001 93

Level of theory	adduct	TS1	Int	TS2	Product
PM6	0.0	9.7	-17.3	-3.1	-11.9
ωB97X-D	0.0	0.4	-14.7	-11.8	-12.9
HF	0.0	3.5	-2.1	-6.6	-12.3
MP2	0.0	-2.0	-20.1	-14.8	-10.0

H_{298}

Level of theory	adduct	TS1	Int	TS2	Product
PM6	0.311 68	0.325 67	0.286 13	0.306 34	0.293 64
ωB97X-D	-1554.350 02	-1554.350 09	-1554.370 96	-1554.368 39	-1554.369 23

Level of theory	adduct	TS1	Int	TS2	Product
PM6	0.0	8.8	-16.0	-3.4	-11.3
ωB97X-D	0.0	0.0	-13.1	-11.5	-12.1

G_{298}

Level of theory	adduct	TS1	Int	TS2	Product
PM6	0.243 35	0.258 37	0.218 74	0.238 87	0.225 98
ωB97X-D	-1554.418 06	-1554.416 35	-1554.437 17	-1554.434 12	-1554.435 91

Level of theory	adduct	TS1	Int	TS2	Product
PM6	0.0	9.4	-15.4	-2.8	-10.9
ωB97X-D	0.0	1.1	-12.0	-10.1	-11.2

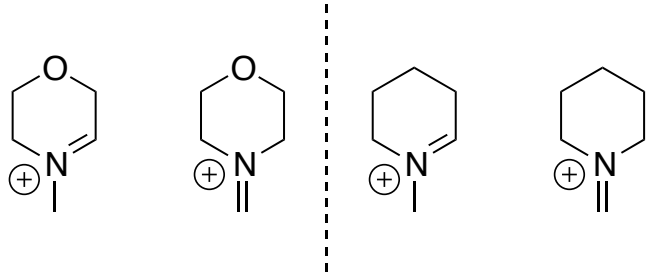
Comment on the results, both energetic and structural, from the various levels of theory.

Various things to note. PM6, DFT, and MP2, all in reasonable agreement on relative energies of *minima*. However, for TS energies, DFT and MP2 are in OK agreement, while PM6 are much higher in energy. Note, though, that MP2 (single points) predict first reaction proceeds without barrier (TS energy lower than reactant). DFT has very, very low barrier. The ring strain in the five-membered cycloalkene makes it very prone to open. Variations in *H* and *G* not particularly exciting.

Note that the "good" levels of theory (DFT and MP2) predict the intermediate to be more stable than the product. MP2 likely overstabilizes (because these catalysts *do* do polymerization). And, we fail to address the full entropy of the product which will have many, many conformations available for the growing chain upon decoordination, contributing to a more favorable free energy.

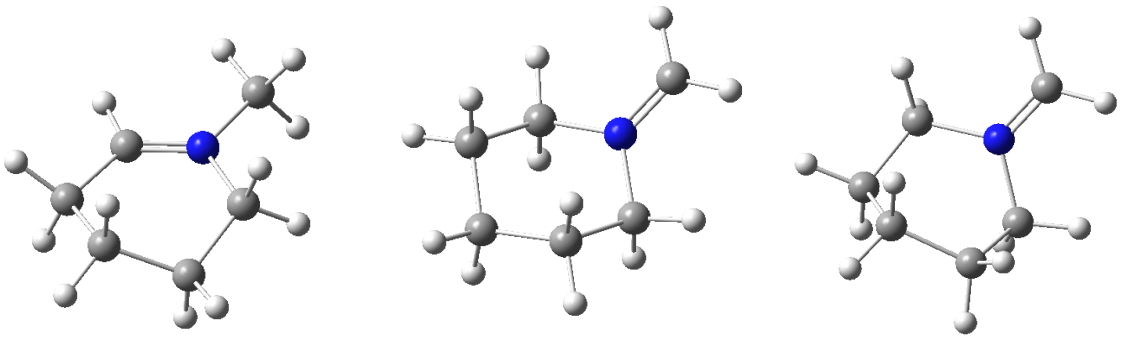
For a full-blown research example of this modeling, see Martinez, H.; Miró, P.; Charbonneau, P.; Hillmyer, M. A.; Cramer, C. J. "Selectivity in Ring-opening Metathesis Polymerization of *Z*-Cyclooctenes Catalyzed by a Second-generation Grubbs Catalyst" *ACS Catal.* **2012**, *2*, 2547 (doi:10.1021/cs300549u).

3. Consider the two pairs of isomeric iminium ions below. In each pair, compute which is more stable (both energy and free energy) at the HF/6-31G(d), MP2/6-311+G(2df,p)//HF/6-31G(d), and M06-2X/6-31+G(d,p). Note (i) there are likely boat-like and chair-like ring forms for each structure that should be separately averaged and (ii) for the MP2 level you will be computing only energies, not free energies.



1 **2** **3** **4**

Discuss the theoretical variations (as a function of level) and the chemical differences (as a function of O vs. CH_2 substitution).



3 **4chair** **4boat**

Pictures for the piperidine-based local minima are provided above. Nothing too remarkable, other than there being chair and boat conformers for the exocyclic isomer. As expected, the chair is lower in energy (see below).

Again, without pretty formatting, putting piperidine system to left and morpholine to right because I like to think of the latter as being a variation on the former (energies in a.u. followed by relative energies in kcal/mol):

E
Level of theory

	3	**4chair**	**4boat**	**1**	**2chair**	**2boat**
HF	-288.439 33	-288.426 36	-288.417 57	-324.234 82	-324.225 10	-324.216 77
MP2	-289.691 73	-289.680 70	-289.672 19	-325.561 80	-325.553 61	-325.545 07
M06-2X	-290.253 75	-290.241 66	-290.233 72	-326.126 37	-326.117 77	-326.109 21

Level of theory

	3	**4chair**	**4boat**	**1**	**2chair**	**2boat**
HF	0.0	8.1	13.7	0.0	6.1	11.3
MP2	0.0	6.9	12.3	0.0	5.1	10.5
M06-2X	0.0	7.6	12.6	0.0	5.4	10.8

G_{298}
Level of theory

	3	**4chair**	**4boat**	**1**	**2chair**	**2boat**
HF	-288.279 85	-288.265 47	-288.257 34	-324.100 37	-324.089 11	-324.081 34
M06-2X	-290.106 28	-290.092 84	-290.085 47	-326.002 88	-325.992 54	-325.984 70

Level of theory

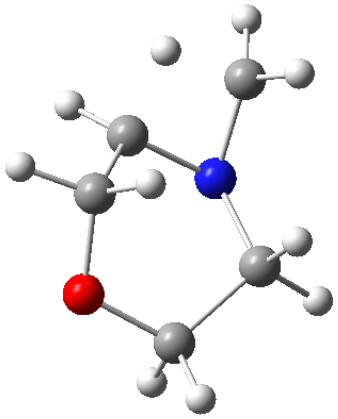
	3	**4chair**	**4boat**	**1**	**2chair**	**2boat**
HF	0.0	9.0	14.1	0.0	7.1	11.9
M06-2X	0.0	8.4	13.1	0.0	6.5	11.4

Nothing too exciting about *E* vs *G*. Chair preferred over boat for exocyclic conformers by 4 to 5 kcal/mol. Endocyclic preferred by about 6 kcal/mol for the morpholine derivative, and by about 8 kcal/mol for the piperidine derivative (presumably an inductive effect associated with oxygen and double bond both being electron-withdrawing, but hard to be certain without deeper analysis). All levels of theory in reasonable agreement for these simple molecules formed from first-row atoms.

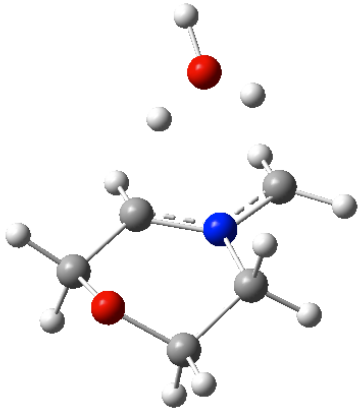
Next, it is observed that refluxing **1** in aqueous solution leads to **2**. Is that consistent with your calculations?

No, the endocyclic double bond is predicted to be more stable. Of course, we've done *gas-phase* calculations in every case...

Find a transition-state structure for the necessary proton transfer at the M06-2X/6-31G(d) level and report its energy relative to the two minima. Next, find a water-catalyzed transition-state structure for the same process using a single water molecule. By how much are the energy and free energy of activation lowered? Why is there a substantial difference between energy and free energy? For your various structures, perform a single-point calculation at the MP2/6-311+G(2df,p) level and compare the HF and MP2 energies of activation to the DFT values. (For purposes of this problem set, do *not* use a continuum solvent model for these calculations.)



uncatalyzed



H_2O-catalyzed

The two transition state structures are shown above (for the morpholine derivative). The energetics are (energies in a.u. followed by relative energies in kcal/mol):

E, uncat
Level of theory

	3	**TS**	**4chair**	**1**	**TS**	**2chair**
M06-2X	-290.238 21	-290.119 56	-290.225 83	-326.110 36	-325.991 74	-326.101 59
HF	-288.522 86	-288.393 01	-288.509 47	-324.336 29	-324.206 21	-324.325 56
MP2	-289.692 96	-289.575 23	-289.682 12	-325.563 54	-325.445 71	-325.555 50

Level of theory

	3	**TS**	**4chair**	**1**	**TS**	**2chair**
M06-2X	0.0	74.5	7.8	0.0	74.4	5.5
HF	0.0	81.5	8.4	0.0	81.6	6.7
MP2	0.0	73.9	6.8	0.0	73.9	5.0

G_{298}, uncat
Level of theory

	3	**TS**	**4chair**	**1**	**TS**	**2chair**
M06-2X	-290.089 80	-289.974 19	-290.075 98	-325.985 92	-325.870 60	-325.975 45

Level of theory

	3	**TS**	**4chair**	**1**	**TS**	**2chair**
M06-2X	0.0	72.5	8.7	0.0	72.4	6.6

The predicted activation free energies are independent of heterocycle and *enormous*. The terrific distortion required to effect the proton transfer helps explain the high energies for the TS structures. HF does a poor job (overestimating barrier, as expected for HF). DFT and MP2 in good agreement. Difference between *E* and G_{298} small.

Turning to the water catalyzed case (obtained by adding H_2O values for *E* and G_{298} to the values in the above table for the minima, while optimizing the TS structure with the water as part of the TS), we have:

E, H_2O-cat
Level of theory

	3•H_2O	**TS•H_2O**	**4chair•H_2O**	**1•H_2O**	**TS•H_2O**	**2chair•H_2O**
M06-2X	-366.611 59	-366.517 12	-366.599 20	-402.483 74	-402.394 68	-402.474 97
HF	-364.576 90	-364.424 94	-364.563 51	-400.390 33	-400.244 73	-400.379 60
MP2	-366.001 99	-365.909 85	-365.991 15	-401.872 58	-401.785 38	-401.864 53

Level of theory

	3•H_2O	**TS•H_2O**	**4chair•H_2O**	**1•H_2O**	**TS•H_2O**	**2chair•H_2O**
M06-2X	0.0	59.3	7.8	0.0	55.9	5.5
HF	0.0	95.4	8.4	0.0	91.4	6.7
MP2	0.0	57.8	6.8	0.0	54.7	5.0

G_{298}, H_2O-cat Level of theory	**3•H_2O**	**TS•H_2O**	**4chair•H_2O**	**1•H_2O**	**TS•H_2O**	**2chair•H_2O**
M06-2X	-366.459 29	-366.350 31	-366.445 47	-402.355 42	-402.251 58	-402.344 94

Level of theory	**3•H_2O**	**TS•H_2O**	**4chair•H_2O**	**1•H_2O**	**TS•H_2O**	**2chair•H_2O**
M06-2X	0.0	68.4	8.7	0.0	65.2	6.6

So, the energies of activation are lowered by about 16 kcal/mol for the piperidine system but closer to 20 kcal/mol for the morpholine system (possibly owing to favorable interactions between the O atom and one of the protons in flight, or, if not favorable, at least not repulsive with the flagpole H at the 4 position). The molecular structure for the catalyzed TS structure looks far more chemically sensible. The *free* energies of activation are reduced by a smaller margin because tying up the water in the TS structure comes with substantial (10-11 kcal/mol) entropic cost compared to two free molecules for the various minima.