

Using PC Model, answer the questions below. If you have questions/issues working on this Problem Set, do please consider using Piazza to address them.

1. In the AMBER and MMFF94 force fields, what are the parameters for the harmonic force constants and equilibrium bond lengths for the bond between an alkyl carbon and a sulfide sulfur? How closely do the two sets of constants agree?

In the AMBER force field (file amber.prm), an alkyl carbon is atom type 1 and a sulfide sulfur (in methionine) is atom type 26. The relevant stretch line from the parameter file is

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bond      1  26      227.0   1.810
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In the MMFF94 force field (file mmff94.prm), an alkyl carbon is atom type 1 and a sulfide sulfur is atom type 15. The relevant bond stretch line from the parameter file is

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bond      1  15   2.893   1.805   C94
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Quick reference to the PC Model manual suggests that the equilibrium bond lengths are 1.801 and 1.805 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 (227.0) kcal/mol-Å² and the units for MMFF94 are (2.893) mdyne/Å. To convert from mdyne/Å to kcal/mol-Å² involves a factor of 143.84 kcal/mdyne-mol-Å, which renders the MMFF94 constant 416.1 kcal/mol-Å². 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 227.0 value used by AMBER, but not in the MMFF94 case, so that the AMBER force constant is really 454.0 kcal/mol-Å², or within about 9% of the MMFF94 value.

Optimize dimethyl sulfide using the AMBER force field. What is the C–S bond distance and what is the total bond stretching strain? Now, fix one C–S bond to a *different* bond length and compute the bond stretching strain. Is it equal to the

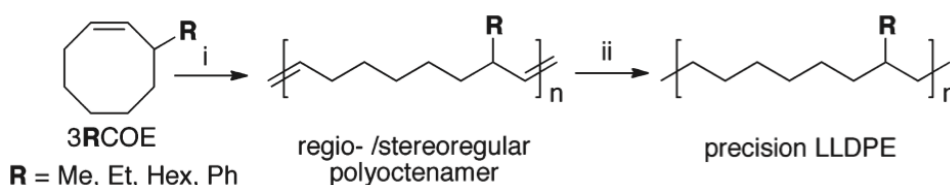
expected value? Explain how you carry out this calculation and how you compute the “expected value”.

Optimized dimethyl sulfide with AMBER has a C–S distance of 1.811 Å and a bond stretching strain of 0.001; the structure essentially adopts the equilibrium bond length and has negligible strain. By selecting the C and S atoms and then selecting Mark/Fix Distance, with a fixed distance of 2.311 Å and a force constant of 100,000, and then performing a minimization, one can get a structure having a C–S bond length of 2.310 Å. Deleting the fixed distance and doing a single point energy calculation gives a stretching strain of 56.57 kcal/mol. If we evaluate $227 \text{ kcal/mol-Å}^2 \times (2.310 \text{ Å} - 1.811 \text{ Å})^2$ we compute 56.52 kcal/mol, which is almost perfect agreement (the difference arises from very small changes in other force field terms).

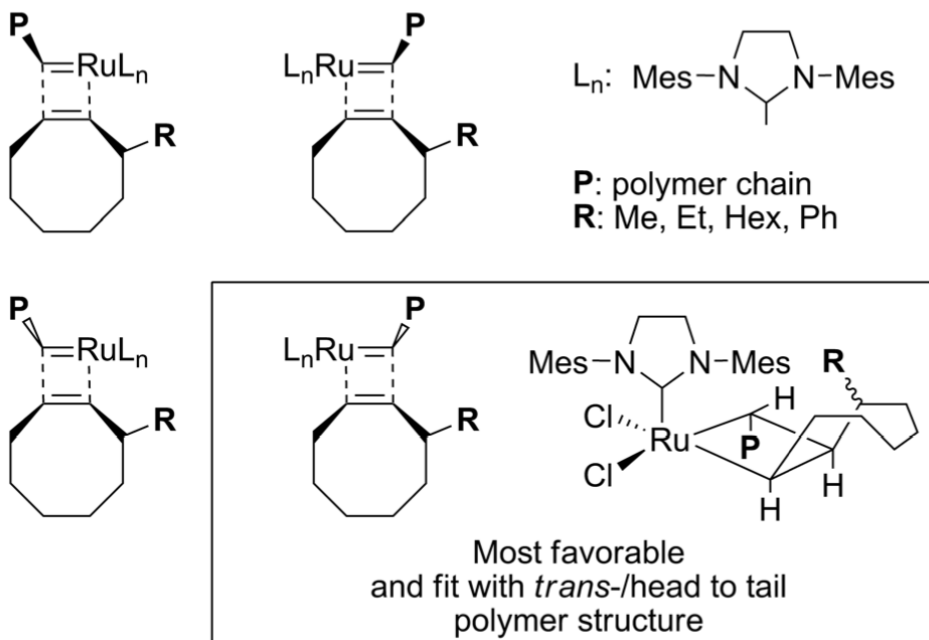
Stretch one C–S bond by the same amount with MMFF94. Is the increase in bond stretch strain for MMFF94 consistent with the AMBER value and the relative force constants for the two force fields? If not, why not?

Since I chose to stretch my C–S bond by 0.499 Å for my AMBER calculations, I need to stretch the C–S bond from 1.808 Å (the equilibrium length in MMFF94) to 2.307 Å. The same procedure as that outlined above gives a stretching strain increase of 29.7 kcal/mol, which is only a bit more than half of the AMBER value. This is not consistent with the harmonic force constants for the two force fields being within 9% 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.

- In Kobayashi, S.; Pitet, L. M.; Hillmyer, M. A. "Regio- and Stereoselective Ring-Opening Metathesis Polymerization of 3-Substituted Cyclooctenes" *J. Am. Chem. Soc.* **2011**, *133*, 5794-5797, the Hillmyer group reported the regio- and stereoselective polymerization of 3-substituted cyclooctenes, which process leads to precision linear low density polyethylene.



The ring-opening metathesis polymerization mechanism involves a [2+2] cycloaddition of the *Z*-cyclooctene with a ruthenium carbene that is the terminus of the growing polymer chain. The observed stereoselectivity implies strong preference for a *trans*-relation of the polymer chain and the cyclooctyl ring on the formed metallocyclobutane, and also a proximal relationship of the 3-substituent with the growing polymer chain, as illustrated on the next page.

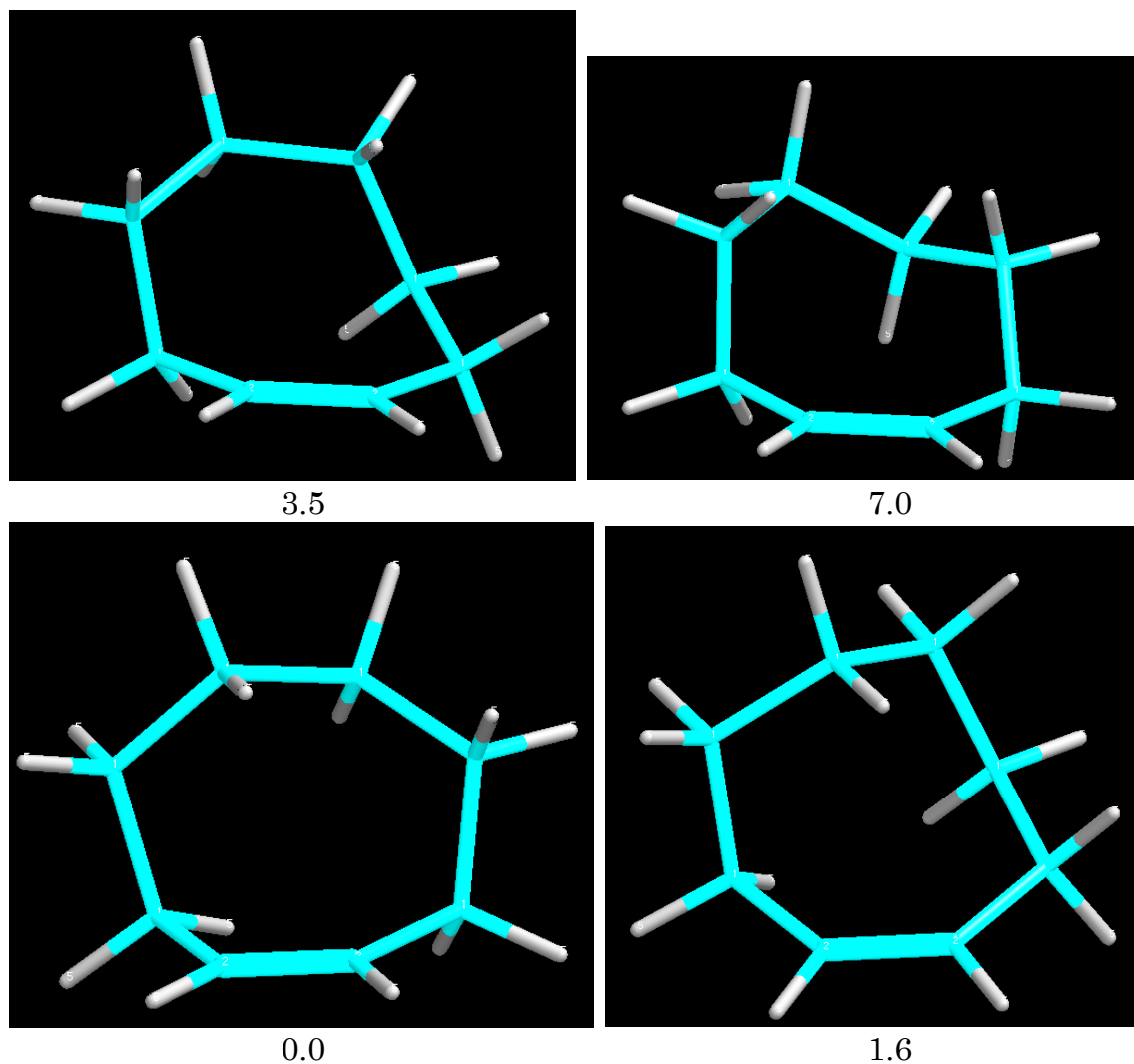


While molecular mechanics is poorly suited to predicting transition-state energetics, in general, it is certainly true that possible transition states will include within them the strain associated with a given conformation of a 3-substituted cyclooctene, above and beyond additional strain associated with non-bonded interactions as the cyclooctene approaches the Grubbs catalyst.

Thus, using the MM3 force field, which should be particularly good for hydrocarbons, carry out a careful search for all possible conformers of *Z*-cyclooctene within 10 kcal/mol of the global minimum (note that enantiomers are not conformers). Report their structures (a picture is fine) and relative energies. Next, carry out a full conformational analysis for 3-methyl-*Z*-cyclooctene. Note that there is a brute force approach that is probably easiest, or there is a systematic approach that is probably more informative and satisfying as a chemist. Let's assume that we're only likely to be interested in conformers within 3 kcal/mol of the global minimum (as otherwise they won't contribute to reactivity in any case)—try to report results from the rational approach, as opposed to the

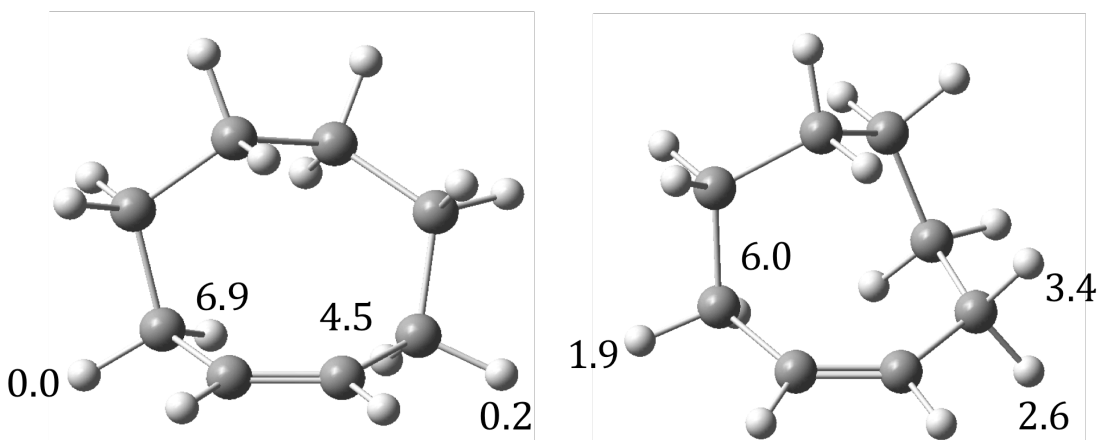
thoughtless brute force approach. Structures and relative energies. Discuss any clear trends that catch your attention.

I used GMMX to stochastically look for all *Z*-cyclooctene conformers. Within 10 kcal/mol of the global minimum, there are only 4 conformers, shown below with their relative energies (MM3, kcal/mol) specified.



Now, with respect to 3-methyl-*Z*-cyclooctene, it is obvious that one could simply run another GMMX calculation (the brute force approach). But, if we're really only interested in conformers within 3 kcal/mol of the global minimum, it seems very unlikely that the two higher energy ring forms will play a role. They already incorporate so much strain that it is unlikely that including a methyl group will somehow be so much worse for one of the low-energy ring conformers compared to a high-energy ring conformer that the

substituted case would play a role. Rather, we could simply put a methyl group at each of the four distinct allylic positions in the two lowest-energy ring forms, and we should have a complete understanding of the accessible geometries.



The relative energies (MM3, kcal/mol) are shown above, labeling each H atom with the relative energy of the 3-methyl-Z-cyclooctene conformer that would be generated by replacing it with a methyl group.

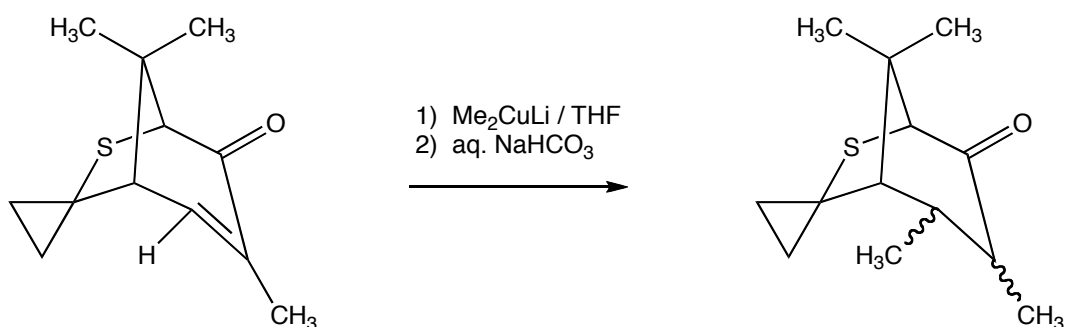
Now, we can't really model even the metallacyclobutane with the force fields available to us in PC Model, but, if you had to use the program to make some estimate of these energies of the four competing TS structures above, describe what you might do. You don't have *actually* to do it—just describe it.

Not really an easy problem at all, at least with the force fields available to us in PC Model. In principle we would need to replace the Ru atom in the metallacyclobutane with some other atom that the force field would accept. For example, a C atom would likely be tolerated, but the C–C distances would be *much* shorter than the Ru–C bonds, so it would be quite an approximation! We'd also likely have to ditch the Cl atoms and hope that only the dimesityl N-heterocyclic carbene is playing a role in steric selection. At that stage, we'd assume all rate-determining transition-state structure energies were directly correlated with metallacyclobutane energies and look for the lowest one.

This is a problem for which quantum mechanics is definitely better. We may look at it again later.

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 $^3J_{\text{HH}} = 4.0$ 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 some 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 2.5 ppm with the doublet coupling $^3J_{\text{HH}} = 7.4$ Hz.



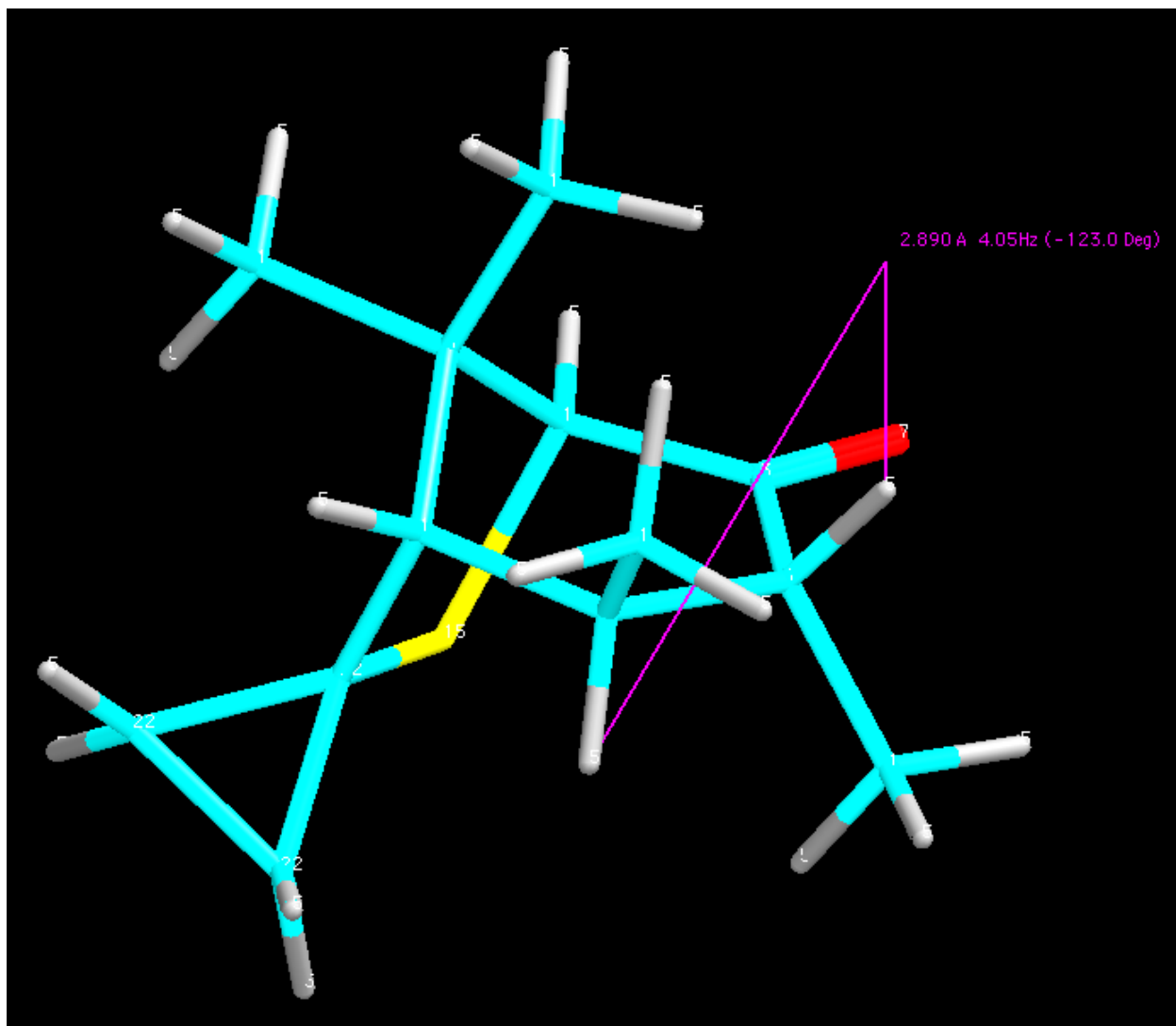
What do you predict to be the integration ratio of the doublet of quartets at 2.3 ppm to that at 2.5 ppm at 298 K? Explain how you arrived at your answer using the MMFF force field.

The integration ratio is about 3:1 for 2.5 ppm vs. 2.3 ppm in the final spectrum.

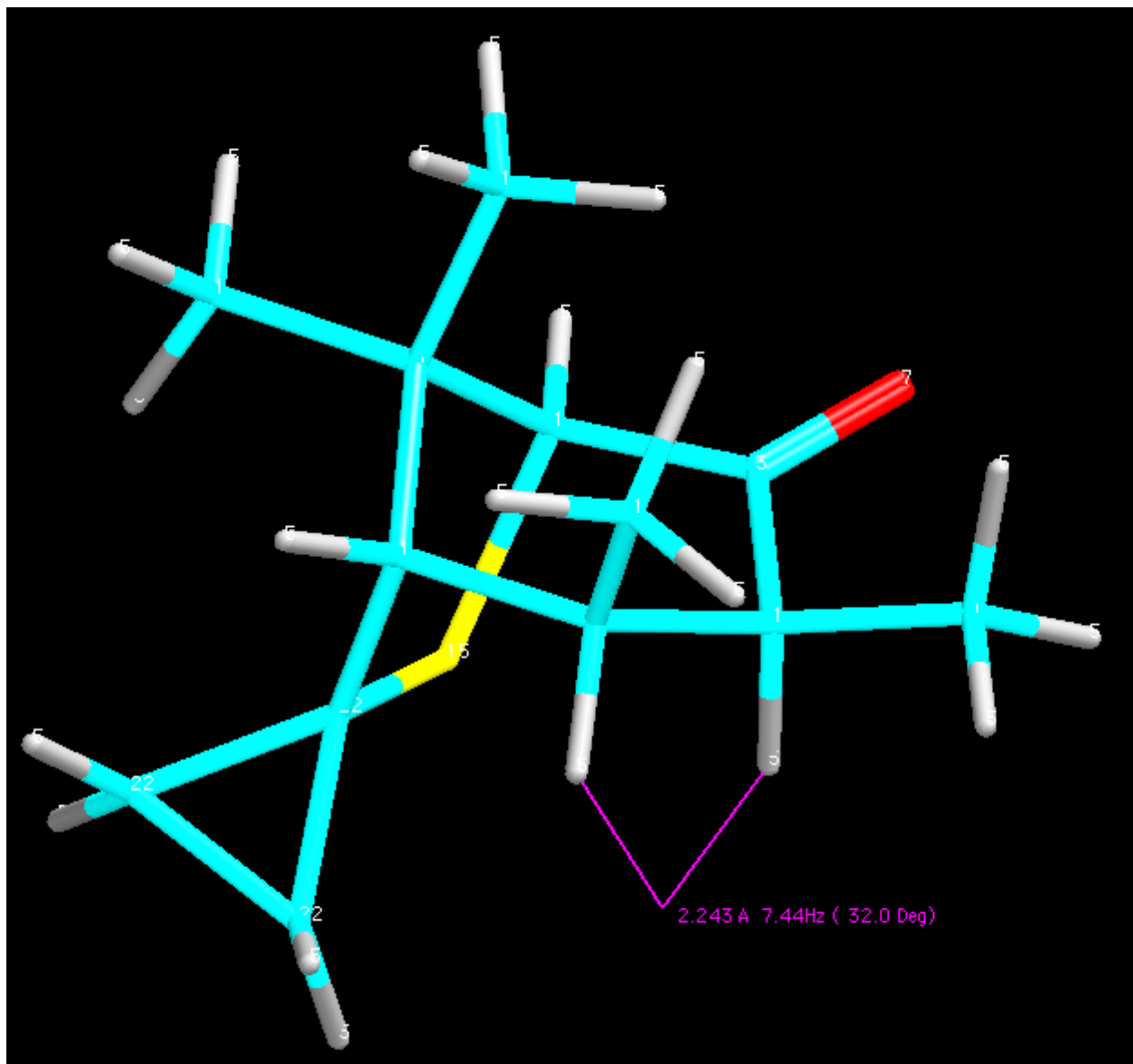
One arrives at this conclusion from noting that there are four possible stereoisomers for the final product, (*exo,exo*), (*exo,endo*), (*endo,exo*), and (*endo,endo*), where the descriptors refer to the orientation of the methyl groups α and β to the carbonyl, respectively. The orientation of the β 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 $^3J_{\text{HH}}$ values for the coupling between the protons at the α and β positions, we obtain (Hz): (*exo,exo*) = 7.4; (*exo,endo*) = 10.9; (*endo,exo*) = 4.0; and (*endo,endo*) = 8.2.

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 63.5 and 62.8 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 3.2, so the integration ratio should be about 3:1.

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.