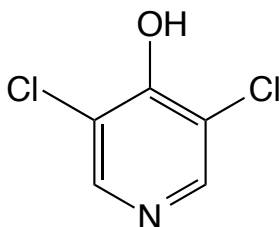


1. What is the aqueous pK_a predicted for the below hydroxypyridine at the M06-2X/6-31+G(d,p) level? For this problem, be certain to include in *all* calculations the keyword `integral(grid=ultrafine)`; use the SMD solvation model to compute aqueous solvation effects. To the extent that there is some error in the computed value, in which direction do you expect the error to be? Justify your answer, and based on that justification, suggest possible improvements in the computational protocol that might be employed, noting the consequences of such improvements from a computational resources standpoint.



If you wanted to measure the pK_a , one approach might be to titrate the phenol dissolved in D_2O in an NMR tube and to follow the chemical shift of the 2 protons on the pyridine ring (the OH proton is exchangeable, and will be washed out by the HOD signal) as a function of added base (or acid). What limiting δ values are predicted for these protons in the conjugate acid and base forms of the molecule? Note that you may find the file in `~cm8021pr/templates` called `tmsnmopt.out` helpful.

If all we do is compute free energies, with the SMD solvation model turned on, at the indicated level of theory, we obtain for 298 K

	Conjugate acid	Conjugate Base	H ⁺
$G(\text{gas})$			-0.009 99
ΔG_{solv}			-0.423 74
$G(\text{aq})$	-1242.491 55	-1242.051 15	-0.433 73
Std state adjustment	0.003 01	0.003 01	0.003 01
Net $G(\text{aq})$ 1 M std sta	-1242.488 54	-1242.048 14	-0.430 72

where the $G(\text{aq})$ values for the conjugate acid and base come directly from calculation, and the value for the proton comes from summing the experimental gas-phase free energy with the experimental solvation free energy. All species take the standard-state

correction, which leads to the final values shown in the last row. At that point, it is simply a question of computing ΔG for the deprotonation (6.1 kcal/mol) and expressing that as a pK_a (equal to $\Delta G / 2.303RT$), which is 4.5. Note that if the C_{2v} symmetry of the conjugate base is not properly accounted for, there will be an error associated with the rotational partition function of $RT \ln 2$, which is about 0.4 kcal/mol, or about 1/3 of a pK unit.

Given that a typical phenol has a pK_a in the 9 range, and that we have substituted the ring with a variety of electron-withdrawing groups, this seems fairly reasonable as a prediction.

In terms of errors, we used a modest basis set, and anions need better basis sets than neutrals (since they have loosely held electrons), so we might expect the products to be more stable with a bigger basis set, leading to a lower pK_a . Other errors could be associated with specific interactions with the first solvation shell that are not well modeled by the continuum approximation, but it is difficult to know a priori which direction such errors might shift the predicted pK_a . In addition, this particular system could have tautomerism issues, so really a population of different tautomeric forms of the conjugate acid should be considered, but, again, it's not clear which direction that might move things.

As for the NMR calculations, the average shieldings computed for the protons in the conjugate acid and base are 22.48 and 22.98 ppm, respectively. Noting the provided TMS shielding of 31.68, those are then *deshieldings* of 9.20 and 8.70, respectively. A titration would be expected to transition from the former to the latter as sufficient base is added to deprotonate the conjugate acid (or vice versa).

2. Congratulations! After years of trying, you have finally succeeded in making the unusual diazirine **1** shown below. You deposit **1** on a neon matrix at 10 K and irradiate it with UV light in the hopes of blowing out N_2 and making carbene **2**. Is the ground state of **2** expected to be a singlet or a triplet? Calculate the energies of both states (at their optimized geometries, of course) at the *mPW1PW91/MIDI!* level to answer this question (note that the MIDI! basis set is accessed using the G98 keyword “*midix*”, *not* “*midi!*”).

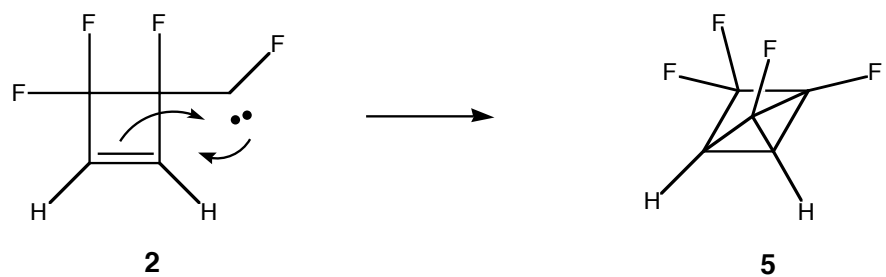
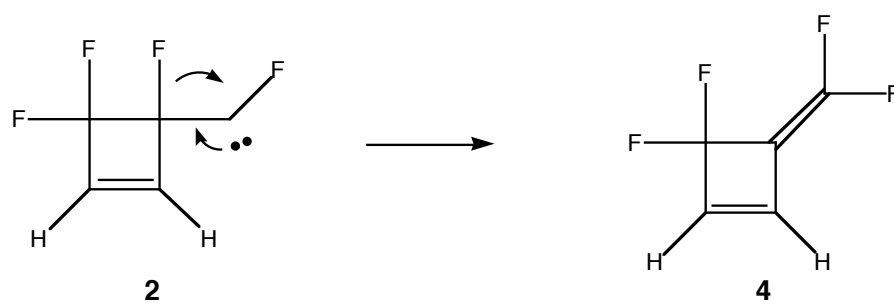
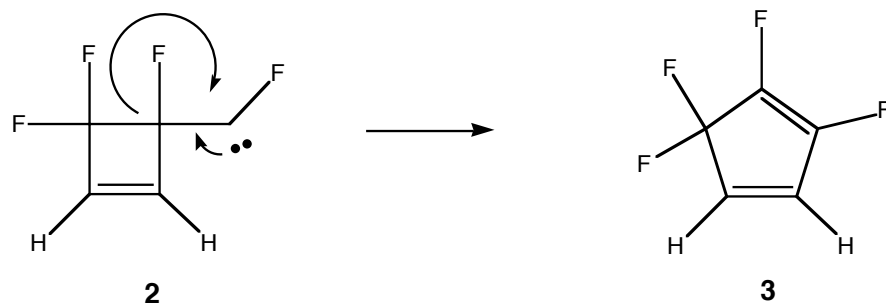
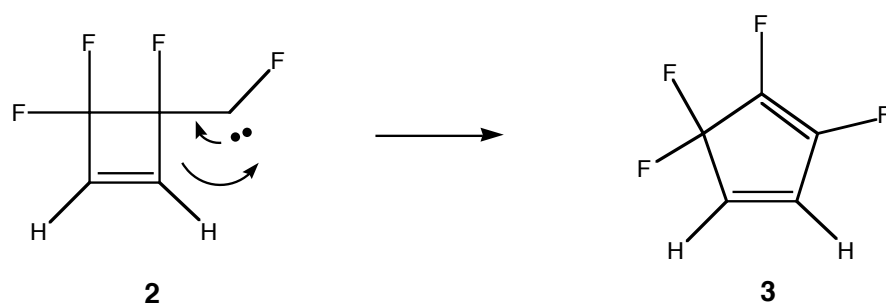
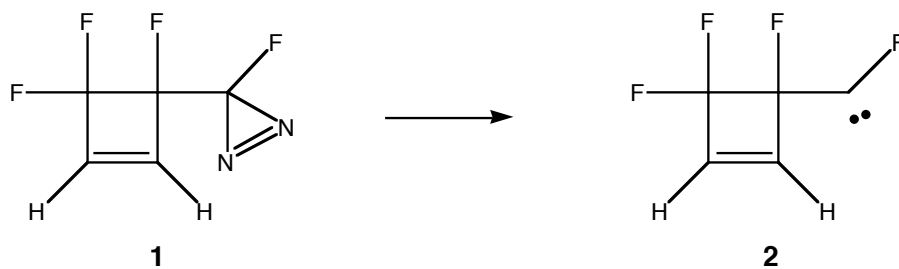
The computed *mPW1PW91/MIDI!* 298 K enthalpies for the singlet and triplet states of **2** are -587.333 52 and -587.316 44 E_h , respectively. The singlet is thus the ground state by 10.7 kcal/mol. (Good thing, since only singlets would be expected to do the

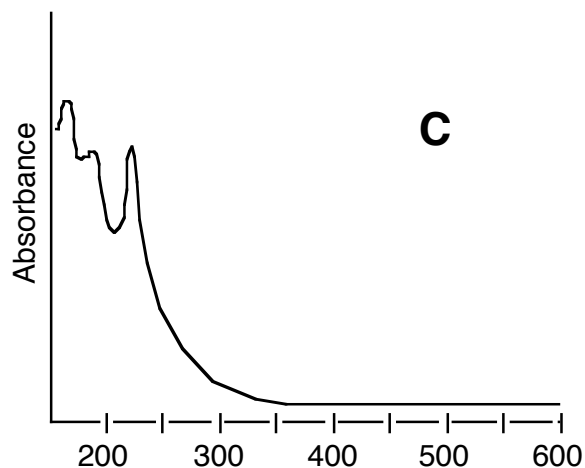
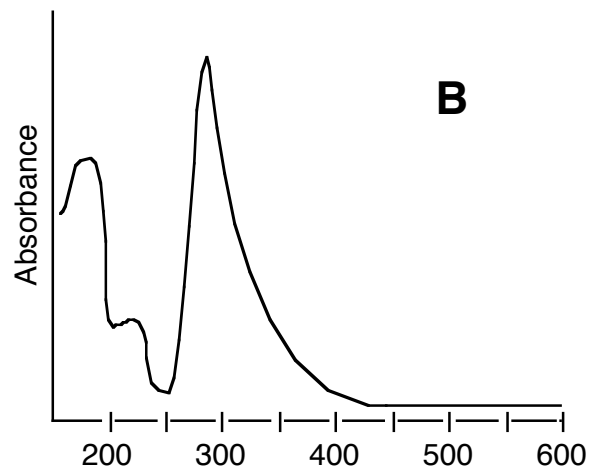
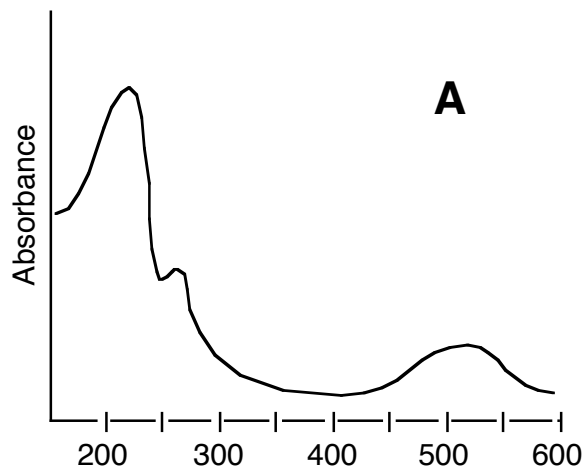
rearrangements that occupy the rest of the problem.) Analysis of E , H_0 , or G_{298} is also perfectly acceptable (all lead to the same conclusion as to the ground state).

From its singlet state, carbene **2** may rearrange in 3 possible ways (two different 1,2-alkyl shifts leading to the same product **3** and a 1,2-fluorine atom shift leading to product **4**) and it may add across the cyclobutene double bond to make the wildly strained polycyclic **5**.

After your initial radiation, you take the UV spectrum **A** shown below. You tune your laser to 510 nm (the long wavelength absorption band in **A**) and blast away again. Afterwards, you observe the new UV spectrum **B**. You tune your laser down to the new “long” wavelength band at 290 nm, and once again flash the matrix. Afterwards, you record the UV spectrum **C**. You then crank your laser down to its lowest setting, 220 nm, and take your last shot at your poor molecule. When you are done, the spectrum is completely bleached (no peaks observed down to 160 nm, the limit of your window). However, when you warm the matrix up and allow the effluent to pass into a mass spectrometer, you record a dominant mass peak at 138 amu.

Using time-dependent density functional theory, predict the 3 longest wavelength UV absorptions for the ground state of **2** and possible products **3-5**. The keywords line to use, after having optimized each geometry, is `# td mpw1pw91/midix guess=read geom=checkpoint`, where you will simply change the checkpoint file each time to reflect which molecule you are computing. Based on these calculations, explain what structures you cycled through in your experiment. In addition, describe, using visualized orbitals, the nature of the 510 nm absorption in structure **A**.





The indicated TDDFT level predicts that singlet structure **2** absorbs at 232 (s), 266 (w), and 513 (m) nm. This is consistent with spectrum A (i.e., you did indeed make the singlet carbene). Structure **3** is predicted to absorb at 178 (m), 214 (w), and 290 (s) nm, consistent with spectrum B (i.e., irradiation at 510 nm converted **2** into **3**). Structure **4** is predicted to absorb at 167 (s), 184 (w) and 227 (m) nm, consistent with spectrum C. Finally, structure **5** is predicted to have all 3 absorptions at energies higher than 160 nm, consistent with no apparent UV spectrum even though a species of mass 138 remains on the matrix.

As you might expect, the 513 absorption in **2** is associated with the HOMO \rightarrow LUMO transition that is an $n \rightarrow p$ excitation (sp^2 lone pair of the carbene to unoccupied p orbital of the carbene).

Now, still at the *mPW1PW91/MIDI!* level of theory, find any *one* of the transition state structures connecting the ground state of **2** to its possible products **3** to **5**. Provide a picture of the structure with key heavy-atom bond lengths labeled. What is the imaginary frequency associated with your TS structure? What is the free energy difference (i.e., ΔG) between **2** and your TS structure? Based on that difference, what is the rate constant for your unimolecular rearrangement that would be predicted from transition-state theory at 10 K? At 298 K? If this reaction were to be the *only* reaction by which **2** reacted, what would be the half-life for disappearance of **2** at 10 K? At 298 K?

The transition state structures are shown in the figure on the next page. Values for ΔG^\ddagger , rate constants, and half lives are in the below table. To convert ΔG^\ddagger to a unimolecular rate constant, we use the TST expression

$$k = \frac{k_B T}{h} e^{-\Delta G^{\ddagger} / RT}$$

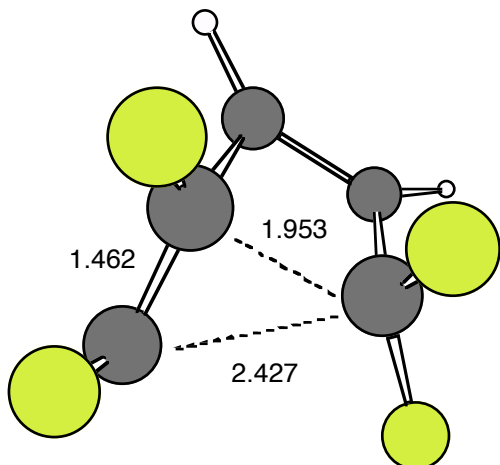
where k_B is Boltzmann's constant, T is temperature, h is Planck's constant, and R is the universal gas constant. For a unimolecular process, the half-life is

$$t_{1/2} = \frac{\ln 2}{k}$$

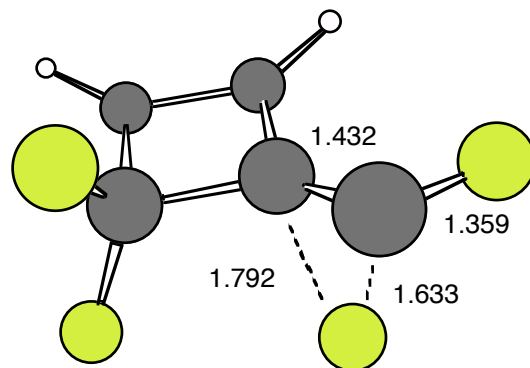
where k is the rate constant.

One subtle point that should be mentioned is that the table below assumes the ΔG^\ddagger value computed at 298 K (the default for G98) to be a constant. We could, in fact, compute it for 10 K using specific keywords to cause G98 to use that temperature, and we would expect it to be different (unless there is a coincidental cancellation between the temperature dependencies of the enthalpies and entropies of activation), but we will not do so, in the interests of simplicity.

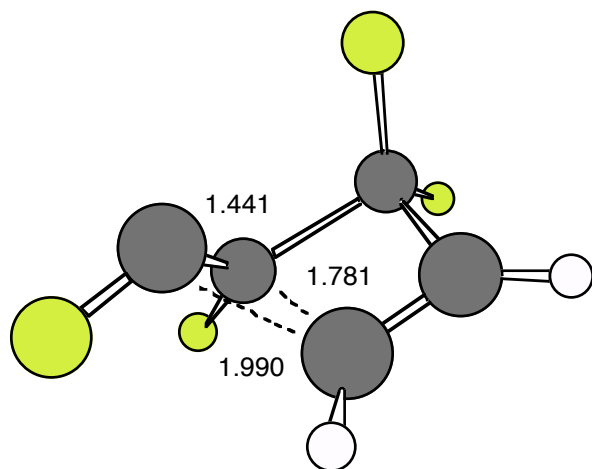
TS structure	ΔG^\ddagger , kcal/mol	k , s ⁻¹ (298 K)	k , s ⁻¹ (10 K)	$t_{1/2}$, s (298 K)	$t_{1/2}$, s (10 K)
2 to 3 path 1	4.6	2.8×10^9	3.7×10^{-89}	2.5×10^{-10}	1.9×10^{88}
2 to 3 path 2	9.9	3.6×10^5	3.6×10^{-205}	1.9×10^{-6}	1.9×10^{204}
2 to 4 path 1	32.8	5.6×10^{-12}	0	1.2×10^{11}	∞
2 to 5 path 1	18.5	1.6×10^{-1}	0	4.2	∞



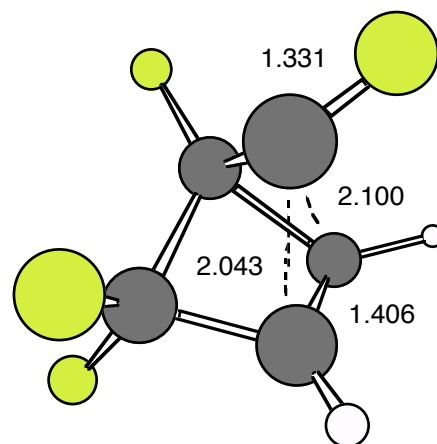
2 to 3 path 1



2 to 4 path 1



2 to 3 path 2



2 to 5 path 1