

5.53 (Molecular Structure and Reactivity I) Problem Sets

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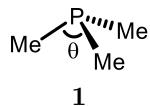
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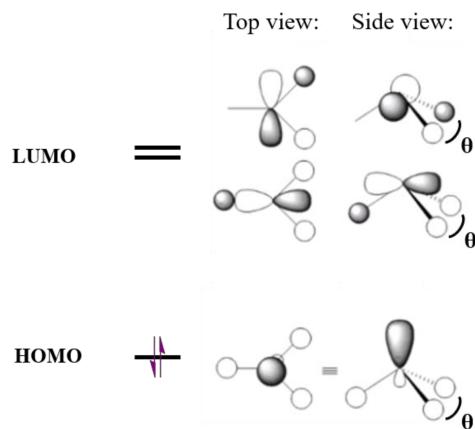
1 Applications of Molecular Orbitals

- 9/25: The questions pertain to the material we have covered from Introduction (Sep 5) to Pericyclic Reactions (Sep 19). For the molecular orbital (MO) diagrams, please draw the MOs with appropriate energy levels, fill in the electrons, and draw cartoons that illustrate the orbital interactions.

1. The geometry of PMe_3 (**1**) is known to be pyramidal.

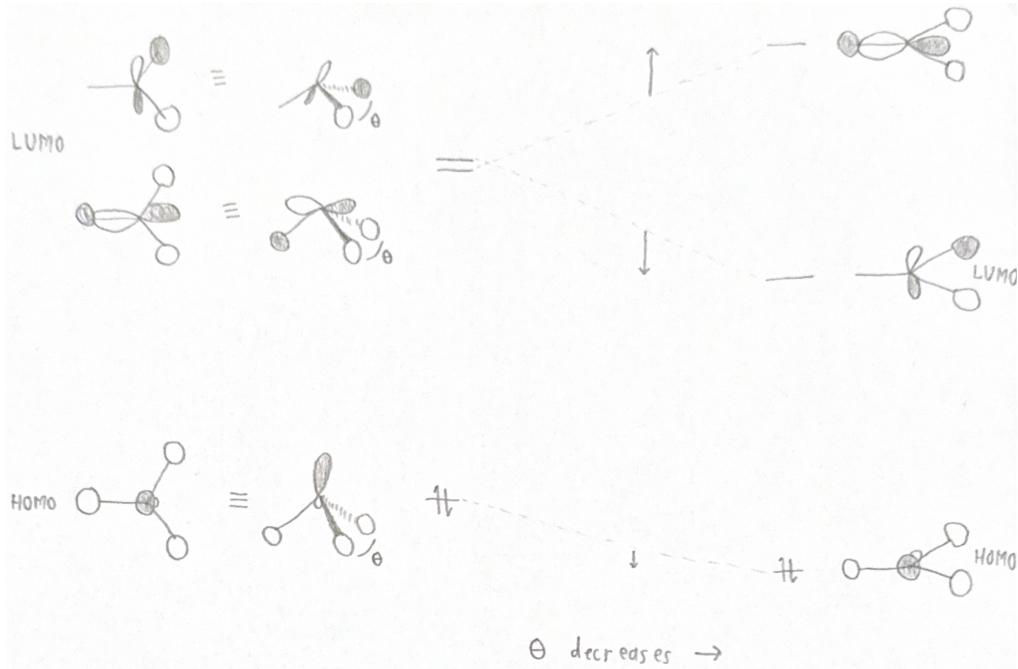


A qualitative MO diagram for the frontier orbitals of PMe_3 can be drawn as follows.



- a) How will the energies of the frontier orbitals change if we decrease one C–P–C angle, denoted as θ , by symmetrically moving the two methyl groups closer to each other? Draw a Walsh diagram for the frontier orbitals to explain. Assume that the bond lengths are unchanged.

Answer. Let's consider the energy changes orbital by orbital, from bottom to top.



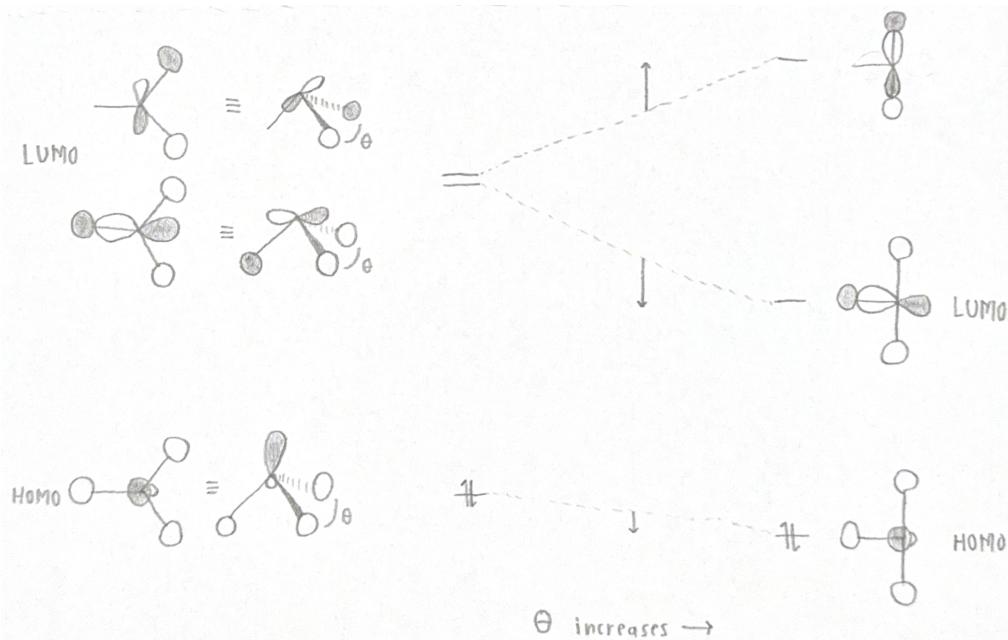
HOMO: As θ decreases with fixed bond lengths, the two methyl orbitals adjacent to θ get closer and begin to participate in a *slightly* stabilizing, secondary interaction. This will cause the HOMO to go down in energy slightly.

Bottom LUMO: As θ decreases, we will observe the same slightly stabilizing secondary interaction as in the HOMO. However, this effect will be dwarfed with increasing primary destructive interference with the phosphorous atom's shaded *p*-lobe. Thus, the energy of this orbital will go up more than the energy of the HOMO went down.

Top LUMO: As θ decreases, we'll gain some destructive secondary interference, but we'll mostly lose primary destructive interference as we approach a primary nonbonding orientation in the nodal plane of the *p*-orbital. Thus, the energy of this orbital will go down on a similar order of magnitude to how much the bottom LUMO went up. \square

- b) How will the energies of the frontier orbitals change if we instead increase θ while maintaining the bond lengths? Draw a Walsh diagram for the frontier orbitals to explain.

Answer. Similarly to part (a), we will also do this analysis orbital by orbital, from bottom to top.

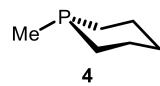
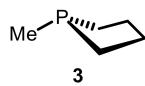
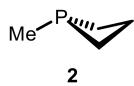


HOMO: As θ increases with fixed bond lengths, the two methyl orbitals adjacent to θ *both* get closer to the methyl on the left side of the diagram. This will induce another *slightly* stabilizing, secondary interaction, but likely a slightly bigger stabilizing interaction than the analogous one in part (a).

Bottom LUMO: Decreasing primary destructive interference between the shaded *p*-lobe and the two unshaded methyl lobes that are moving results in a net stabilizing interaction that is more significant than the slightly stabilizing interaction in the HOMO.

Top HOMO: Increasing primary destructive interference leads to a similarly significant destabilizing interaction. \square

- c) Rank the relative nucleophilicity and electrophilicity of the following molecules, and rationalize your hypotheses.



Answer. θ is unstrained in **4**, θ is slightly decreased in **3**, and θ is more decreased in **2**. Additionally, a higher energy/more destabilized HOMO will make a species more nucleophilic, and a lower energy/more stabilized LUMO will make a species more electrophilic. Thus, all we need to answer this question is the MO diagram in part (a).

Since the HOMO gets more stabilized as θ decreases,

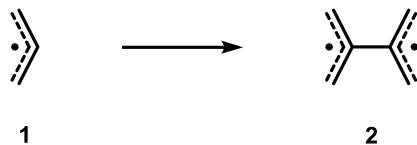
4 is the most nucleophilic, then **3**, then **2**.

Since the LUMO also gets more stabilized as θ decreases,

2 is the most electrophilic, then **3**, then **4**.

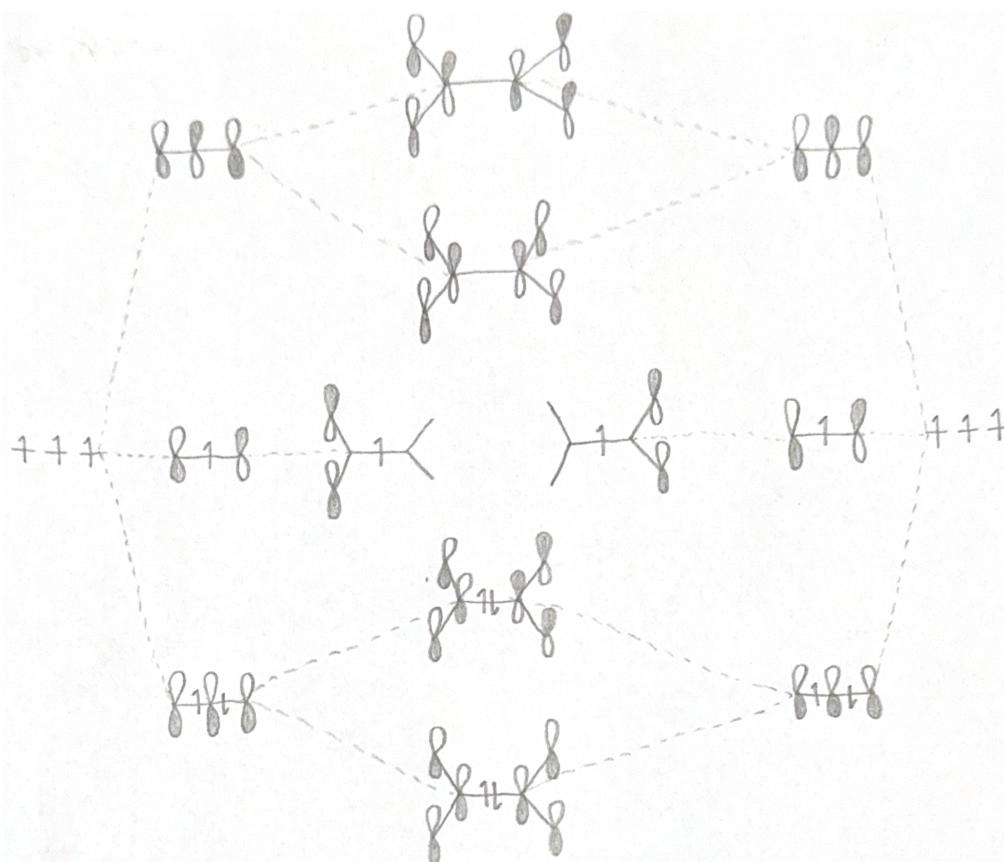
□

2. Consider the combination of two allyl fragments (**1**) joined at the center carbons, leading to diradical (**2**).



- a) Construct a π MO interaction diagram for **2** that predicts the symmetries of the combined MOs and their energies relative to carbon p -orbitals. Please assume that only interactions between AOs on adjacent atoms are significant.

Answer.



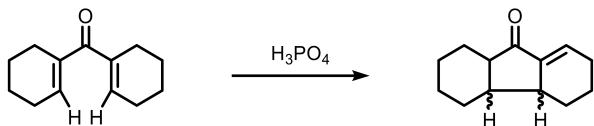
Since this MO diagram only considers π -orbitals, we begin by drawing two sets of standard allyl MOs that we will subsequently mix. Each set of allyl MOs is composed of three p -orbitals. Additionally, since there are 2 π -electrons in the double bond and 1 π -electron in the radical, each set of π -MOs is occupied by three electrons.

As we begin mixing, we only mix MOs of similar energies. In this case, that means we only mix MOs directly across. Note that we do *not* mix the middle MOs because the problem statement tells us that only MOs with “adjacent atom” interactions should mix, and these MOs have no electron density in the center where the σ -bond forms. Additionally, note that we only have electron density on one side or the other (rather than both) because if we had it on both, that would imply that we are adding or subtracting wavefunctions; in other words, the mixed orbitals are of the form $\psi_1 \pm \psi_2$ and the degenerate orbitals are of the form ψ_1, ψ_2 . \square

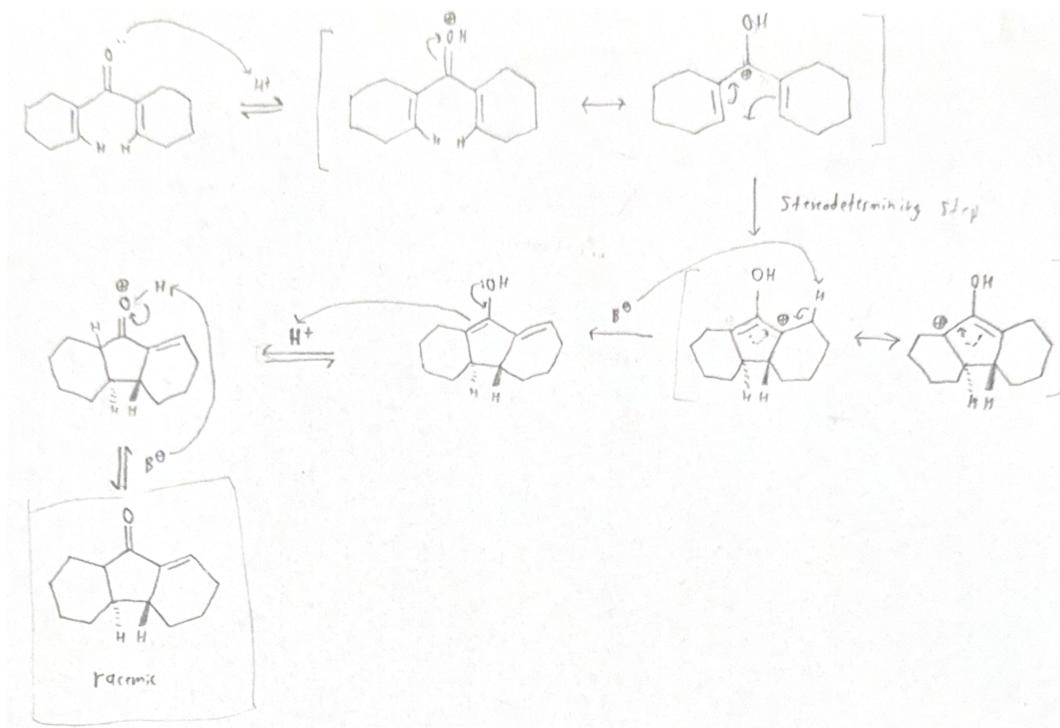
- b) Can the two radical centers delocalize via resonance? Explain using the MO diagram from part (a).

Answer. [No.] Per the MO diagram, we still have a diradical in the HOMO, and each radical electron is localized in an MO on one side of the molecule. \square

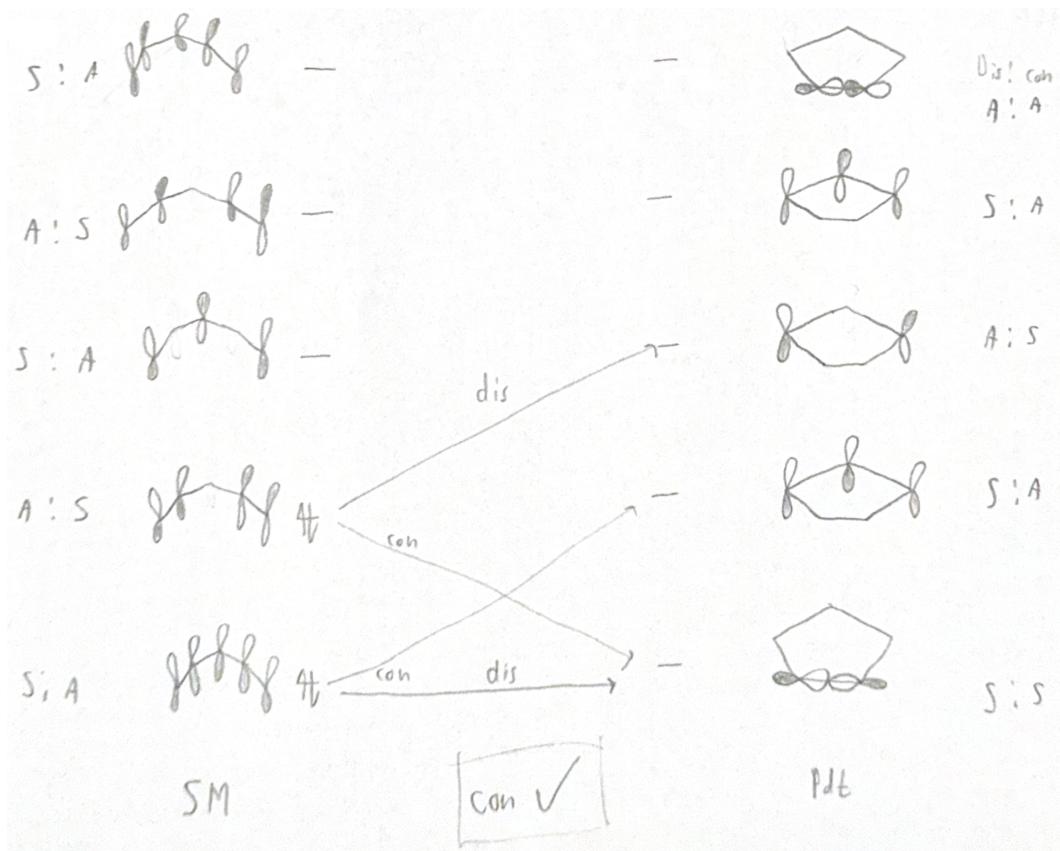
3. Predict the stereochemistry of the product and rationalize your answer based upon MO theory.



Answer.



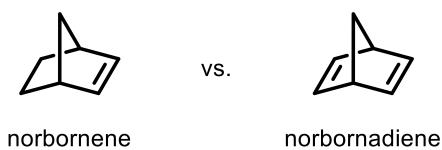
The stereodetermining step is a cationic 4π electrocyclization, more commonly known as a **Nazarov cyclization**. Note that a few steps are necessary before the cyclization to activate the substrate, and a few are necessary afterwards to convert to the final product.



The reason that the electrocyclization occurs in a conrotatory fashion is that the thermal symmetry-allowed transitions do not move electrons up in energy levels, whereas the thermal symmetry-allowed disrotatory transitions do and hence are disfavored. Note that I did not show the R groups for simplicity.

Additional notes: This problem can also be solved using FMO and rotation. □

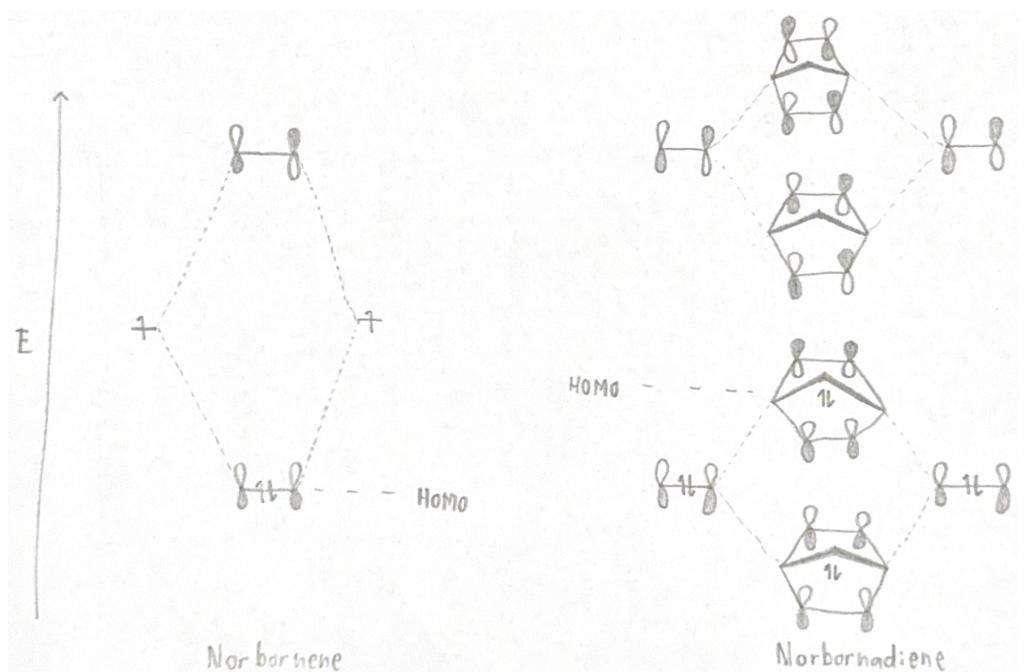
- Norbornadiene is known to be more reactive towards electrophiles than norbornene.



- Rationalize this difference using an MO diagram.

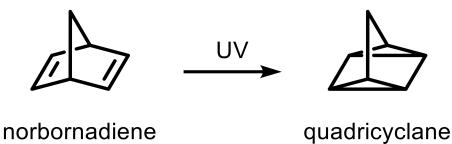
Answer. Norbornene has two p -AOs that mix into two π -MOs: One bonding and one antibonding. Norbornadiene has two pairs of these π -MOs that can then weakly re-mix through space across the molecule to form four new MOs.

After mixing, the second-lowest of these MOs (the new HOMO) will be higher in energy than the unmixed original π -MO (the old HOMO and, coincidentally, norbornene's HOMO). Essentially, this through-space mixing causes norbornadiene to have a higher HOMO than norbornene. As discussed in Q1c, species with a higher HOMO are more nucleophilic, and hence more reactive toward electrophiles.



□

- b) Norbornadiene derivatives can be converted to quadricyclane derivatives under UV irradiation. Quadricyclanes are highly strained molecules, yet they are thermally stable.

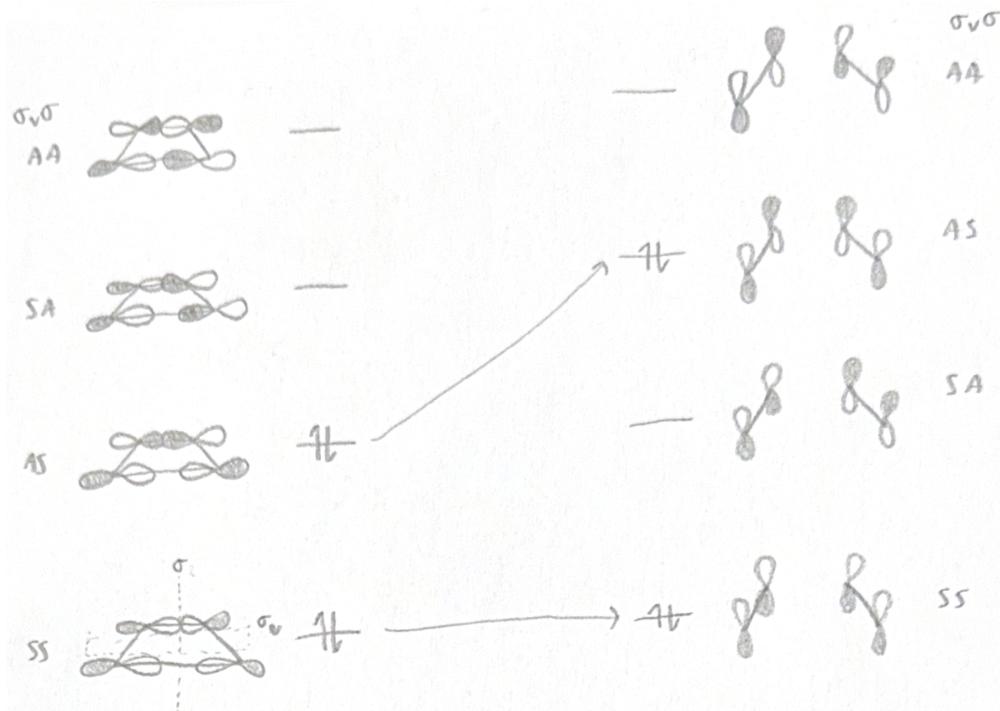


Provide a frontier MO analysis^[1] to explain why quadricyclane is thermally stable.

Answer. The reaction depicted above is a photochemical [2 + 2] cycloaddition.

To justify why the product is *thermally* stable, let's correlate the product orbitals to the starting material orbitals. Note that in doing so, we will identify the symmetry of each molecular orbital by the two persistent symmetry operations, as suggested by Anslyn and Dougherty (2006, p. 880). Namely, we will look at the σ -plane discussed in class, and a perpendicular σ_v plane running from left to right across the page. Note also that the remainder of the quadricyclane and norbornadiene rings outside of the 4-membered ring will be omitted from the following diagram for clarity.

¹Per Jonathan's 9/24 Canvas announcement, we can use *any* MO analysis discussed in lecture; in particular, we are not restricted to Fukui's FMO.

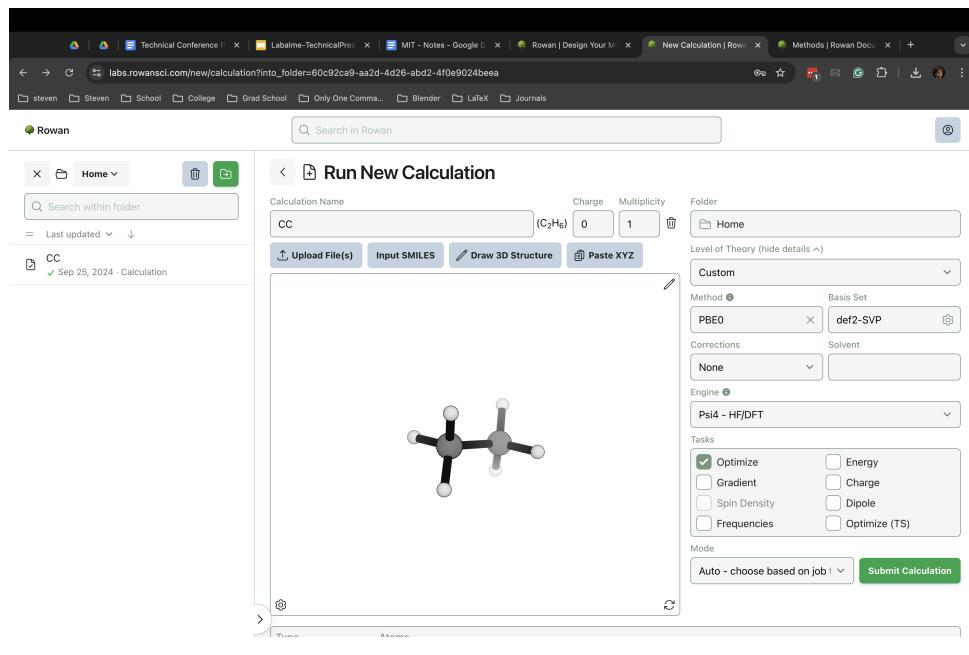


As such, we can see that a thermal cycloreversion is forbidden/disfavored because it would involve creating a high-energy excited state of norbornadiene. \square

5. Please use computational tools to complete this question. We will be using a browser-based quantum chemistry platform ([Rowan](#)) for this course.

- Create an account on Rowan (<https://rowansci.com/>) using your MIT email.
 - To learn how to submit a job on Rowan, please watch this video tutorial: <https://docs.rowansci.com/web-interface/run-a-simple-job> and/or read this overview: <https://docs.rowansci.com/web-interface/submit/geometry-optimization>.
 - More information on how to use Rowan (as well as additional tools) can be found here: <https://docs.rowansci.com/web-interface>.
- Ethane (H_3CCH_3).
 - Using any means, build a molecular model for ethane in Rowan. Then, perform a geometry optimization using the PBE0 functional and the def2-SVP basis set. Take a screenshot of the webpage before submitting the job and paste it here.
 - Note: this job should not take more than 1 minute to run (not including queue time). If it takes significantly longer, consider adjusting your initial bond lengths/angles.

Answer.



- ii. Convert the optimized structure into Cartesian (XYZ) coordinates and paste them here.

Answer.

```
C -0.75677857 -0.05411065 0.03565919
C 0.75677857 0.05411065 -0.03565919
H -1.15393947 -0.71157723 -0.75360372
H -1.23964754 0.92846958 -0.08395828
H -1.08879565 -0.46588635 1.00165110
H 1.08879566 0.46588615 -1.00165118
H 1.15393946 0.71157739 0.75360359
H 1.23964755 -0.92846954 0.08395849
```

- iii. What is the calculated optimized C–C bond distance? What is the H–C–H bond angle(s)?^[2]

Answer. C–C bond distance: 1.519 Å.

H–C–H bond angle: 107.26°.



- c) Ethyl cation (H_3CCH_2^+).

- i. Using any means, build a molecular model for the ethyl cation in Rowan. Then, perform a geometry optimization using the PBE0 functional and the def2-SVP basis set. Take a screenshot of the webpage before submitting the job and paste it here.

- Note: this job should not take more than 1 minute to run (not including queue time). If it takes significantly longer, consider adjusting your initial bond lengths/angles.

Answer.

²Per Jonathan's 9/24 Canvas announcement, provide at least 4 significant figures for bond lengths and angles. If you previously had issues obtaining these values from Rowan, please try again as the problem should be resolved now. If you are still unable to get 4 significant figures from Rowan, contact Jonathan.

The screenshot shows a web-based molecular modeling interface. At the top, there's a navigation bar with various tabs like 'Technical Conference', 'Labalme-Technic...', 'MIT - Notes - Gov...', 'Rowan - Design Y...', 'New Calculation', 'Methods | Rowan', and 'ethyl cation smile...'. Below the navigation is a search bar labeled 'Search in Rowan'.

The main area is titled 'Run New Calculation'. It has fields for 'Calculation Name' (set to 'Ethyl Cation'), 'Charge' (1), 'Multiplicity' (1), and 'Folder' (set to 'Home'). There are buttons for 'Upload File(s)', 'Input SMILES', 'Draw 3D Structure', and 'Paste XYZ'. A 3D ball-and-stick model of an ethyl cation is displayed.

On the right, under 'Level of Theory', it says 'Custom' with 'Method' set to 'PBE0' and 'Basis Set' to 'def2-SVP'. Under 'Corrections', 'None' is selected. Under 'Engine', 'Psi4 - HF/DFT' is chosen. Under 'Tasks', 'Optimize' is checked, while 'Energy', 'Gradient', 'Spin Density', 'Frequencies', 'Charge', 'Dipole', and 'Optimize (TS)' are unchecked. The 'Mode' dropdown is set to 'Auto - choose based on job'. At the bottom right is a green 'Submit Calculation' button.

- ii. Convert the optimized structure into Cartesian (XYZ) coordinates and paste them here.

Answer.

```
H -1.22084801 0.85147887 0.51800484
C -0.64953900 -0.05423031 0.27448674
H -0.17606995 0.13377943 -0.93834042
H -1.18064873 -1.01496471 0.24418216
C 0.70652007 0.01092307 0.02934683
H 1.28037984 -0.89670040 -0.20069381
H 1.24020579 0.96971405 0.07301367
```

□

- iii. What is the calculated optimized C–C bond distance? What is the H–C–H bond angle(s)?

Answer. C–C bond distance: 1.380 Å.

H–C–H bond angle: 118.43° and 105.89°.

□

- d) Now, using qualitative MO arguments based on your calculations, discuss at least two factors contributing to the differing C–C bond lengths in ethane vs ethyl cation.

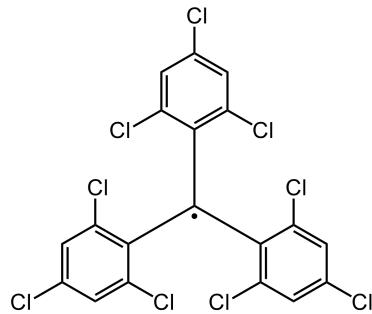
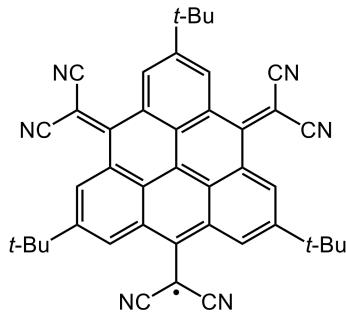
Answer. Due to hyperconjugation, there is donation from the adjacent C–H σ-bond into the carbocation's empty *p*-orbital that forms a 3c-2e bond. This donation increases the bond order of the C–C bond, shortening it compared to ethane. Additionally, the *sp*²-like bond angles mean — per the hybridization index — that the hybrid orbitals have more *s*-character and hence will be shorter.

□

2 Reactive Intermediates

10/16: The questions pertain to the material covered from Cations (Sep 24) to Selectivity (Oct 8).

- The radicals below are known to be **bench-stable**, meaning they don't readily dimerize or get quenched by oxygen. Rationalize this observation for each.

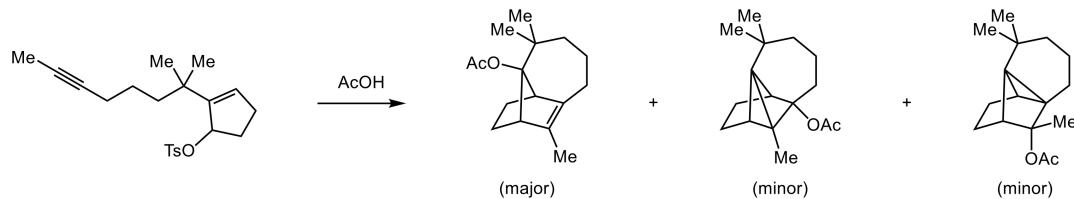


Answer. A bench-stable radical — also known as a persistent radical — is a radical that is thermodynamically high-energy (as all radicals are) but kinetically slow to react. Persistent radicals typically have some mixture of resonance stabilization and steric blocking.

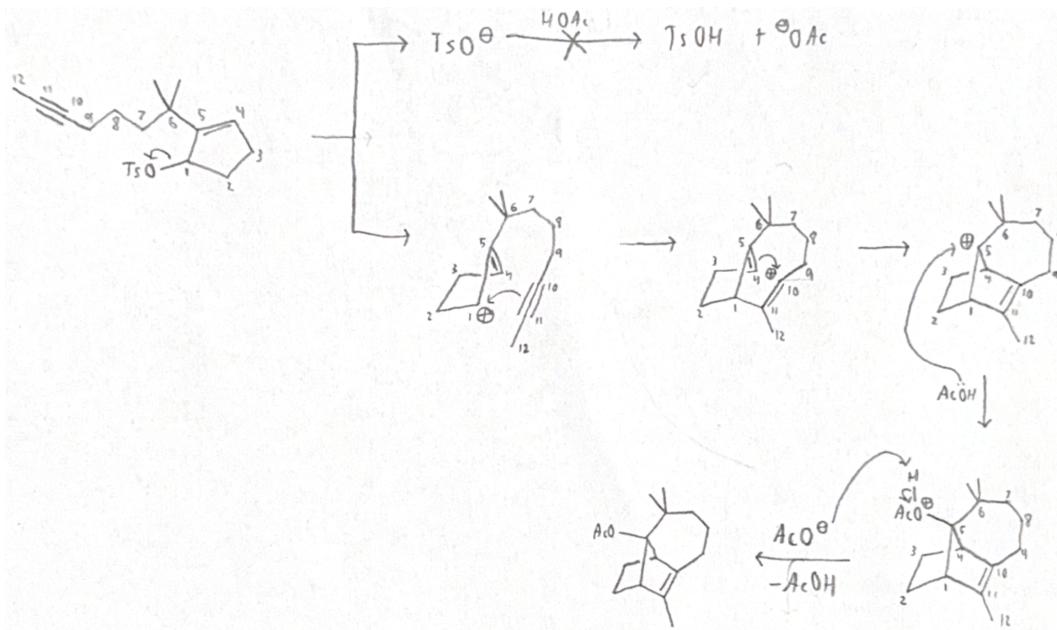
Left radical: This radical has an *extreme* amount of resonance delocalization among both the polycyclic π -system and the nitrile electron-withdrawing groups. By my count, resonance structures indicate that there should be partial radical character at 19 distinct atoms in the molecule. Thus, the spin density map should be so distributed that no one site has enough radical character to react in a kinetically efficient manner.

Right radical: Due to steric inhibition of resonance — see Anslyn and Dougherty (2006, p. 282) — this radical cannot efficiently delocalize because the conformation of the trichlorophenyl rings in space (i.e., the “paddle wheel” topology) prevents full planar double bond formation. Thus, there is more radical character on the central carbon, as drawn. However, the paddle-wheel groups sterically block access to this site, once again preventing kinetic dimerization. \square

2. a) Propose a reasonable arrow-pushing mechanism that explains the formation of the major product in the reaction below.



Answer.



Due to its high degree of resonance stabilization, tosylate is a very good leaving group. Additionally, the cation created by a tosylate departure is both secondary and resonance-stabilized. As such, I propose that the reaction mechanism will be initiated by tosylate leaving. The majority of the tosylate ions in solution will then continue to exist as tosylate (instead of deprotonating acetic acid, for example) because tosylic acid is much stronger than acetic acid.

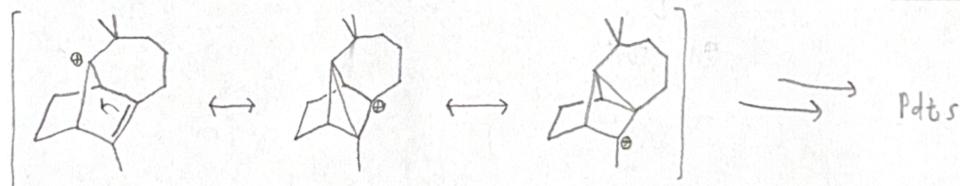
Once the first intermediate is formed, it seems like it could do a cationic [3 + 2] cycloaddition. However, such cycloadditions are thermally forbidden by the Woodward-Hoffmann rules (which we could also quickly see by drawing the HOMO of the alkyne and the LUMO of the allylic cation and observing the partial phase mismatch). As such, I propose that the allylic cation reacts intramolecularly via a two-step Gassman-type [3 + 2] non-pericyclic “cycloaddition.” Intramolecular “cycloaddition” would likely outcompete external nucleophilic attack both because it’s an intramolecular process (greater local concentration), and there aren’t any particularly *great* nucleophiles in solution. Additionally, while I have drawn the first step proceeding from a particular resonance structure, in reality, either symmetric resonance structure could react to form the same ensuing intermediate.

After the Gassman-type cycloaddition, a homoconjugation-stabilized cation will be left on the norbornene analog. This cation can then react with the best (and highest concentration) nucleophile in solution, which will be protonated acetic acid. Acetic acid has $pK_a = 4.76$ (in H_2O), so it will likely largely exist in the protonated form regardless of the solvent in which we run this reaction. Theoretically, tosylate could also react in this step to add in, but there’s much less of it, it’s a much worse nucleophile, and we’ve already discussed in class how homoconjugation speeds up tosylate departure from that position in norbornene by 5-11 orders of magnitude; so even if tosylate did add in, that process would likely be highly reversible.

Once acetic acid adds in, its proton will be highly acidic and easily deprotonated by a base in solution. This could be the solvent, but it could also be AcO^- , TsO^- , or AcOH . Among these choices, I feel like AcO^- would do the deprotonation the most often because even though there's not much of it present, there will still be more of it than TsO^- (and it's more basic than TsO^-) and for AcOH_2^+ , $pK_a = -6.1$. This deprotonation yields the final product. \square

- b) Suggest how the minor products could be formed and draw the key intermediate(s) involved.

Answer.



I suggest that the final cation before AcOH adds in has partial nonclassical, 3c-2e character. It will still favor the homoconjugation-stabilized form drawn in part (a) — accounting for why that gives the major product — but a Mulliken partial charge on the other carbons could also lead to AcOH addition to those resonance forms followed by deprotonation, as drawn in part (a). \square

3. Which of the following two compounds is more acidic (lower pK_a)? Compare the acidity of the protons indicated red. Rationalize your answer.

a)



Answer. Neither esters nor amides are particularly enolizable since the lone pairs from the adjacent oxygen/nitrogen atoms compete with the resultant anion to delocalize into the carbonyl; this is an example of the resonance saturation effect described on Anslyn and Dougherty (2006, p. 282). However, the ester will be more acidic than the amide because the oxygen holds onto its electrons more tightly than the amide, thus sapping less of the carbonyl's potential ability to withdraw electrons.

An alternative perspective to take is that the amide is more stable before deprotonation, and the two species have similar stabilities afterwards; therefore, it takes more energy to deprotonate the amide. □

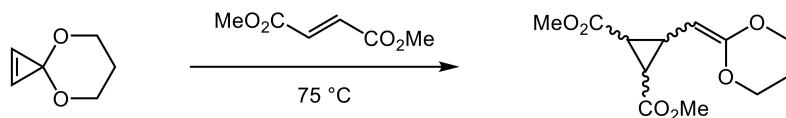
b)



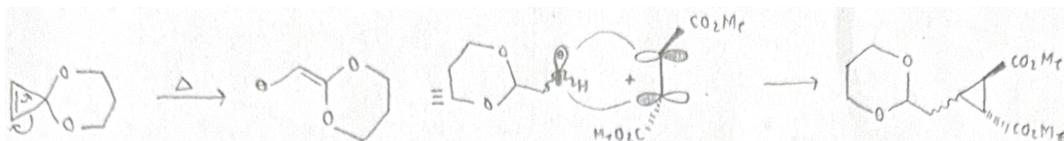
Answer. This regime is also governed by a resonance saturation effect. In both lactone and ester, the non-carbonyl oxygen will be sp^2 -hybridized so that one of its lone pairs can conjugate with the carbonyl (specifically, the carbonyl's π^* -orbital). However, in the drawn conformation of the ester, the other oxygen lone pair can also delocalize through $n_O \rightarrow \sigma_C^*$ donation. This secondary interaction is not possible in the lactone, which is conformationally locked such that the other oxygen lone pair points away from the carbonyl's σ^* -orbital. The net effect is that the carbonyl in the lactone is less electronically saturated than the carbonyl in the ester, so the lactone anion can delocalize more effectively into the lactone carbonyl. But then the lactone can more readily stabilize the conjugate base, so the lactone is more acidic.

We can also take the perspective that the lactone is more destabilized because the n_O dipole and the C=O dipoles align and repel each other; the products, again, have similar stabilities. □

4. a) Suggest a reasonable mechanism for the following transformation.



Answer.



The elevated temperature suggests — as a first step — either a homolytic bond cleavage (as in the case of AIBN) or some kind of pericyclic reaction. The cyclopropene bonds will likely be very strained, but all the same, the bonds will likely not be as weak as AIBN's bonds. As such, I propose a retro-anionic 4π electrocyclic reaction as a first step. This will move the double bond to its final place and produce a singlet carbene. Moreover, the carbene will remain a singlet because of the π -donor ability of the oxygen heteroatoms through the conjugated system. More accurately, when the oxygen atoms and π -system mix with the carbene **D**-orbital, they stabilize themselves and raise the energy of the empty **D**-orbital, making it more energetically favorable to pair electrons in the **C'**-orbital. There would also be an argument to make — based on class content — that conjugation with the π -bond favors the triplet state, but I believe that the π -donor ability from two oxygens (as described above) will outweigh this competing effect.

This singlet carbene can then be approached (on either face!) by the other reactant. I predict that the carbene will react with its HOMO since it is receiving electron density from a π -donor, while the other reactant will react with its LUMO since it has two adjacent ester EWGs. With the phasing match of a nonlinear approach, the next step will be a chelotropic $[2 + 1]$ cycloaddition, forming our product. The *trans*-EWGs of the alkene will yield a *trans*-product, but — as mentioned above — we will get some of both diastereomers with respect to the other bond because the carbene has two faces open to nonlinear approach. □

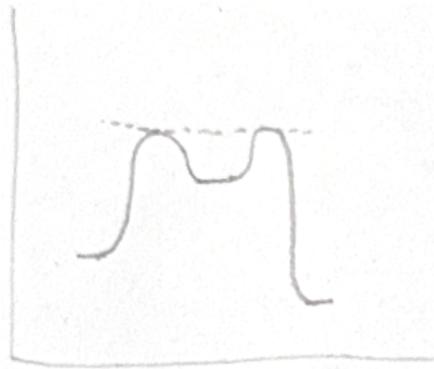
- b) Discuss the stability of the intermediate(s) and predict the stereochemistry of the product.

Answer. See part (a).

5. Draw potential energy diagrams for each of the following situations. Use dashed horizontal lines to indicate equivalent energy levels.

- a) A single substrate can undergo two reactions with equal rates but different product stabilities. What reaction conditions would you use if you wanted a mixture of products? What reaction conditions would you use if you wanted a single product, and which product would you expect?

Answer.



Draw the substrate at an arbitrary energy level. Since both reactions have equal rates, draw humps with equal ΔG^\ddagger to both sides of it, one for each reaction. Then curve the humps down to products at different energy levels.

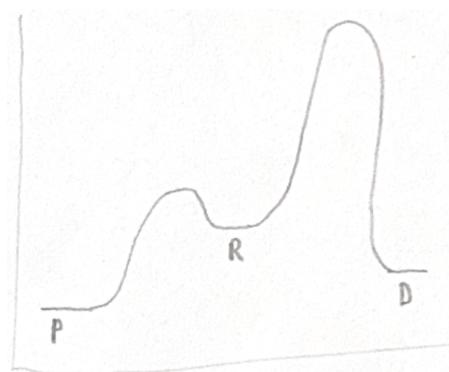
If I wanted a mixture of products (i.e., the kinetic products irreversibly formed through the energetically equivalent transition states), I would use short reaction times and low temperature.

If I wanted a single product (i.e., the thermodynamic product formed irreversibly along with a reversibly formed alternate product), I would use long reaction times and high temperature.

It follows that I would expect the more stable product to be formed at the end. □

- b) The formation of a kinetically stable radical from a precursor and dimerization of that radical.

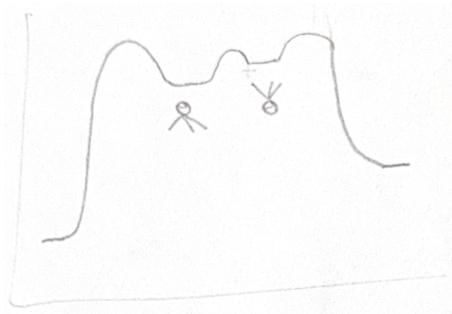
Answer.



The precursor (P) goes over a slight energy hump to become a relatively higher energy radical (R). Once the radical is isolated, it is kinetically stable, meaning that there must be a *very* high energy barrier to it forming the dimer (D). Note that the dimer would still be more *thermodynamically* stable than the radical (because persistent radicals are still *radicals*; they don't want to exist). Also, we would probably need more information to determine *for sure* whether the dimer or precursor is more thermodynamically stable, but I drew it higher in energy because I feel like in a number of systems (envisioning TEMPO, for instance), the steric blocking groups would seriously clash in a dimer, making it less thermodynamically stable than whatever precursor we're using (e.g., TMP). □

- c) The stereoselective protonation of a tertiary carbanion.

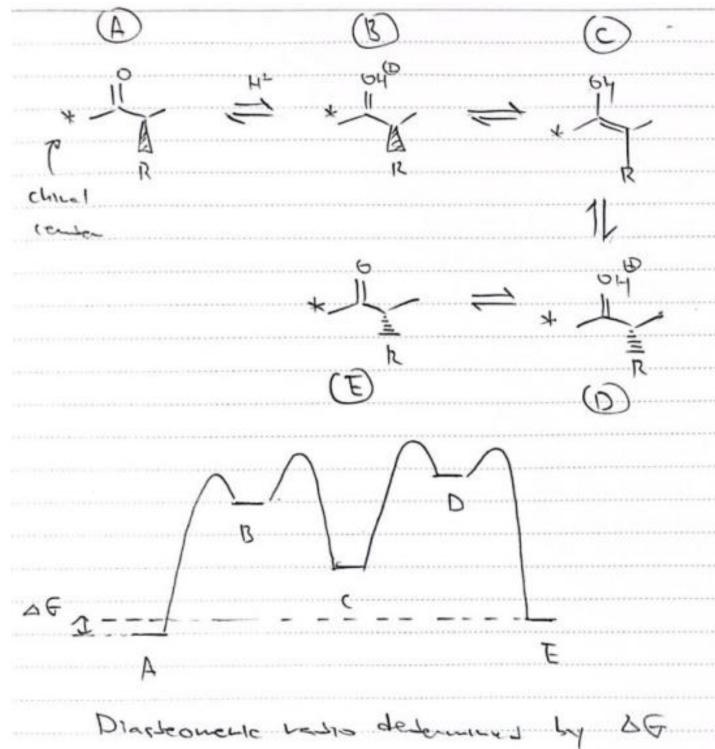
Answer.



Since it can generate two stereoisomers, the tertiary carbanion must be able to be protonated on either of its prochiral faces. As such, I propose a Curtin-Hammett regime in which the tertiary carbanion is in equilibrium between two inversion states. The inversion state that is slightly higher in energy will be the one that brings the more sterically bulky groups closer together. From here, we will have protonation that will likely be fairly low-barrier (as it gets rid of the reactive intermediate anion), and likely result in fairly equal-energy products. However, the higher energy anion will have its bulky groups closer together, meaning that the anion is more exposed for *slightly* easier protonation, and it will also probably form the *slightly* less stable product since, again, the bulky groups will be closer together. This is like Curtin-Hammett Scenario 2. □

- d) Starting from one pure diastereomer, the epimerization of the alpha position of a ketone under acidic conditions to form a mixture of products.

Answer.



□

3 Noncovalent Interactions and Thermodynamics

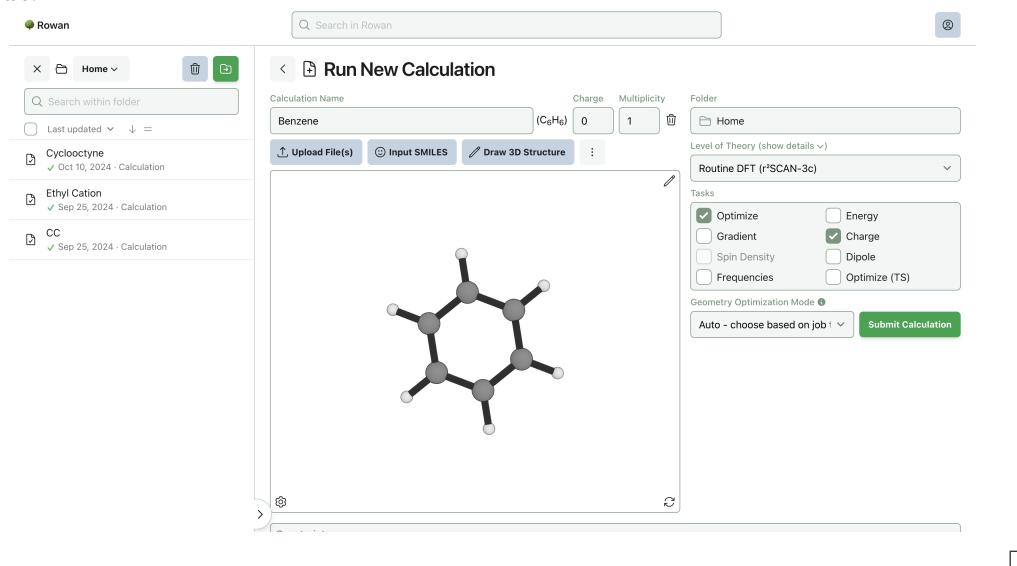
11/14: The questions pertain to the material covered from Noncovalent Interactions (Oct 24) to Isotope Effects (Nov 5).

- The π - π interaction in aromatic systems plays an important role in the fields of chemistry and biology. It affects the crystal packing of organic molecules, molecular recognition processes, and the three-dimensional structures of proteins and DNA.

a) Please use Rowan to complete this question.

- Using any means, build a molecular model for benzene in Rowan. Then, perform a geometry optimization and charge calculation using the r²SCAN-3c method. Take a screenshot of the webpage before submitting the job and paste it here.
- Note: this job should not take more than 1 minute to run (not including queue time). If it takes significantly longer, consider adjusting your initial bond lengths/angles.

Answer.



□

- Convert the optimized structure into cartesian (XYZ) coordinates and paste them here.

Answer.

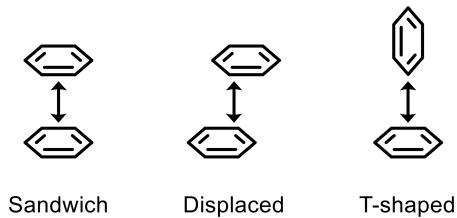
```
C 1.08186398 0.87624363 -0.02492904
C 1.29957353 -0.49892653 -0.02069362
C 0.21782415 -1.37512819 0.00423309
C -1.08186402 -0.87624412 0.02492904
C -1.29957346 0.49892716 0.02069361
C -0.21782322 1.37512844 -0.00423311
H 1.92529173 1.55932611 -0.04436360
H 2.31283908 -0.88800382 -0.03682784
H 0.38774005 -2.44726076 0.00753188
H -1.92529254 -1.55932713 0.04436366
H -2.31283985 0.88800436 0.03682783
H -0.38773950 2.44726073 -0.00753189
```

□

- How are the charges distributed on the molecule?

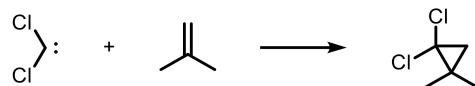
Answer. The Mulliken partial charges are all concentrated symmetrically on the carbon atoms, -0.150 on each carbon and +0.150 on each hydrogen. □

- b) As mentioned in class, benzene rings can interact through various geometries. Explain why the displaced and T-shaped configurations may exhibit lower energies compared to the sandwich geometry. In your discussion, include considerations of polarization effects and electrostatic interactions.



Answer. It is more favorable for benzene rings to interact through quadrupole-type noncovalent interactions. In sandwich stacking, two regions of negative charge touch each other. On the other hand, in both displaced and T-shaped stacking, a region of partial negative charge (the center of the ring) can interact with a region of partial positive charge (the edge of another ring). \square

2. The reaction of dichlorocarbene with isobutylene is known to be one of the exceptions where the reaction has a negative activation enthalpy (ΔH^\ddagger).

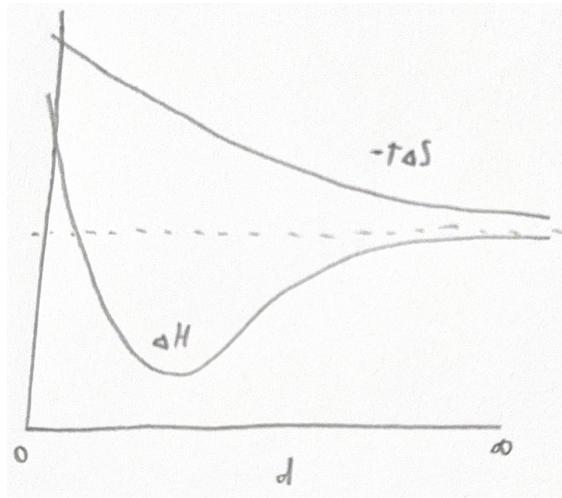


- a) Consider the reverse reaction. Conduct a thought experiment in which we gradually pull dichlorocarbene away from isobutylene. How would ΔH vary with distance? How would ΔS vary with distance? Draw an energy diagram depicting both ΔH and $-T\Delta S$ as functions of distance on a single plot. Assume that ΔH and ΔS are zero at infinite distance.

Answer. The forward reaction proceeds via a side-to-side interaction of either the carbene HOMO and alkene LUMO, or the carbene LUMO and alkene HOMO. Without the loss of generality, let's consider the case of the carbene HOMO and alkene LUMO. As these orbitals mix, we get enthalpically favorable steric stabilization like in the silylene example from the 10/24 NCIs lecture. Thus, considering the reverse reaction, entering higher vibrational states of the two ‘new’ C–C bonds eventually leads to the two species eventually “pinging” apart, as in the $t\text{Bu}-\text{Cl}$ example from the 10/29 equilibria lecture. As we pull apart the ‘starting materials,’ we consistently decrease orbital mixing, which is consistently enthalpically disfavorable; we do not later get any type of favorable process such as solvation.

Thus, ΔH varies with distance (d) by decreasing from zero at $d = \infty$ to the product bond length, and then increasing to some finite (not infinite) value. So the potential is vaguely Lennard-Jones like, in that attraction gets more favorable when the distance gets closer, up to the point when the carbene nucleus starts getting too close to the alkene nuclei. However, it never goes to ∞ because — unlike in the $t\text{BuCl}$ example — $d = 0$ does *not* correspond to two nuclei being on top of each other, which would be infinite energy.

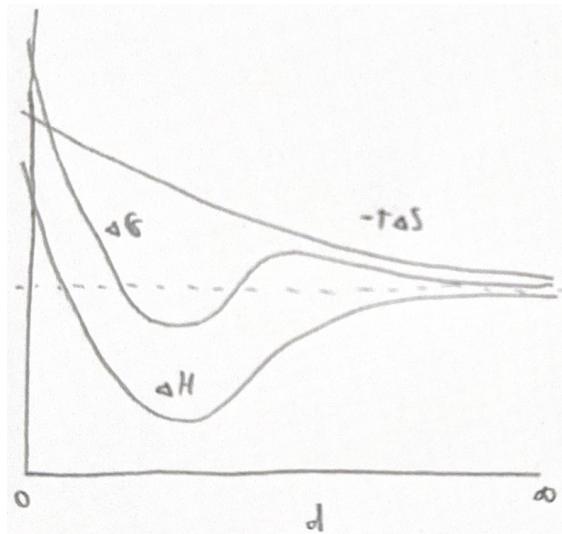
$-T\Delta S$ increases as distance decreases, accelerating as the species get closer together. This is because the entropy drops as we go from two molecules to one, probably by close to 30 e.u.. Essentially, we are forming a highly-ordered single-molecule product that is much less entropically favorable.



□

- b) If ΔH dominates at a short distance, and ΔS dominates at a large distance between the molecules, how would ΔG change as a function of distance? Draw an energy diagram for ΔG on the plot from part (a).

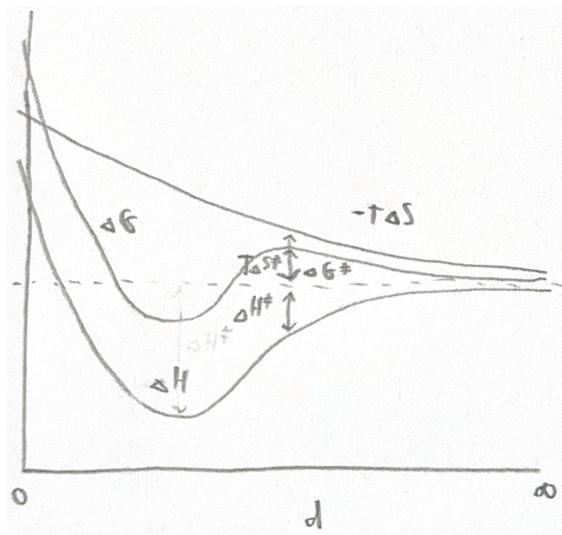
Answer. As the molecules get farther apart, ΔG would be negative at first (due to ΔH) and then positive later (due to ΔS).



□

- c) Indicate ΔG^\ddagger , ΔH^\ddagger , and $T\Delta S^\ddagger$ on the diagram and explain why this reaction exhibits a negative activation enthalpy.

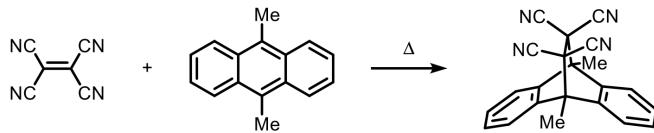
Answer.



By definition, the activated complex is the highest energy point on the potential *energy* surface along the reaction coordinate. Thus, I have drawn all three arrows at the peak in ΔG .

The reaction exhibits a negative activation enthalpy because at the activated complex, the change in enthalpy ΔH^\ddagger from separate species ($\Delta H^\ddagger = 0$ at $d = \infty$) is negative. □

3. The following table presents the experimentally measured kinetic data for a Diels-Alder reaction between tetracyanoethylene (TCNE) and 9,10-dimethylanthracene (DMA).



<i>solvent</i>	[TCNE](M)	temperature (°C)	<i>k_{exp}</i> (M ⁻¹ s ⁻¹)
toluene	8.44 × 10 ⁻⁴	13.5	2.29 × 10 ³
		25.0	2.81 × 10 ³
		39.4	3.79 × 10 ³
		40.2	3.81 × 10 ³
1,2 – dichloroethane	8.90 × 10 ⁻⁴	12.4	9.60 × 10 ⁴
		24.9	8.90 × 10 ⁴
		36.1	8.36 × 10 ⁴
		43.1	8.13 × 10 ⁴

- a) Use this data to determine the observed activation enthalpy (ΔH^\ddagger) and activation entropy (ΔS^\ddagger) for the reaction in the following solvents. Use Excel or a similar program to answer the question, and give your answers in units of kcal mol⁻¹ and/or e.u. (cal K⁻¹ mol⁻¹).

- i. Toluene.

Answer. To solve for ΔH^\ddagger and ΔS^\ddagger using experimental temperature-rate constant data, we will use an Eyring plot. This method works off of the following linearization of the Eyring equation

$$\ln\left(\frac{kh}{\kappa k_B T}\right) = -\frac{\Delta H^\ddagger}{R} \left(\frac{1}{T}\right) + \frac{\Delta S^\ddagger}{R}$$

where $k = k_{\text{exp}}$, $h = 6.626 \times 10^{-34}$ J s is Planck's constant in the appropriate units, κ is the transmission coefficient, $k_B = 1.381 \times 10^{-23}$ JK⁻¹ is the Boltzmann constant, T is the temperature in Kelvin, and $R = 1.9872 \times 10^{-3}$ kcal mol⁻¹ K⁻¹ = 1.9872 e.u. is the ideal gas constant. In accordance with the second fundamental assumption of transition state theory — that any molecule that makes its way to the transition state will then proceed onto the product barrierlessly — we choose $\kappa = 1$. Thus, our raw temperature-rate constant data become

1/T (K ⁻¹)	ln(kh/k _B T)
3.49 × 10 ⁻³	-21.682
3.35 × 10 ⁻³	-21.517
3.20 × 10 ⁻³	-21.265
3.19 × 10 ⁻³	-21.262

Performing a linear regression, we can determine that

$$-\frac{\Delta H^\ddagger}{R} = -1440 \text{ K}$$

$$\boxed{\Delta H^\ddagger = 2.86 \text{ kcal/mol}}$$

$$\frac{\Delta S^\ddagger}{R} = -16.7$$

$$\boxed{\Delta S^\ddagger = -33.2 \text{ e.u.}}$$

□

ii. 1,2-dichloroethane.

Answer. Apply an analogous technique to Q1ai: Start by manipulating the data

$1/T (\text{K}^{-1})$	$\ln(kh/k_B T)$
3.50×10^{-3}	-17.943
3.36×10^{-3}	-18.061
3.23×10^{-3}	-18.161
3.16×10^{-3}	-18.211

and then perform a linear regression

$$-\frac{\Delta H^\ddagger}{R} = 789 \text{ K}$$

$$\boxed{\Delta H^\ddagger = -1.57 \text{ kcal/mol}}$$

$$\frac{\Delta S^\ddagger}{R} = -20.7$$

$$\boxed{\Delta S^\ddagger = -41.1 \text{ e.u.}}$$

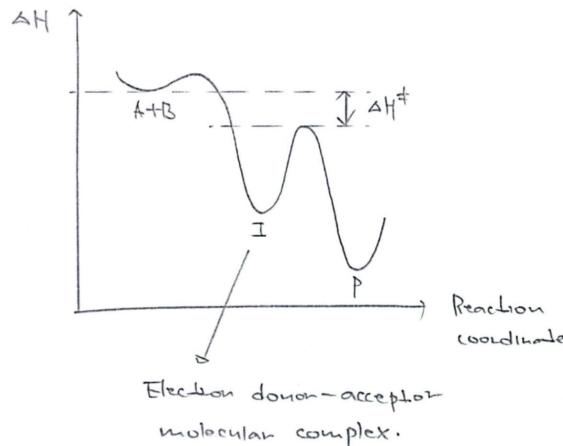
□

- b) Considering that ΔH^\ddagger is positive for most reactions, what is notable about the observed ΔH^\ddagger value(s) in the above case(s)?

Answer. When the reaction is run in 1,2-dichloroethane, there are is a *negative* enthalpy of activation as in Q2. □

- c) Both experiments and theory support the existence of an intermediate between the starting materials and the product in this reaction, known as an electron donor-acceptor molecular complex. Draw a potential energy diagram with ΔH (change in enthalpy) on the y -axis to rationalize the observed abnormality in part (b).

Answer.

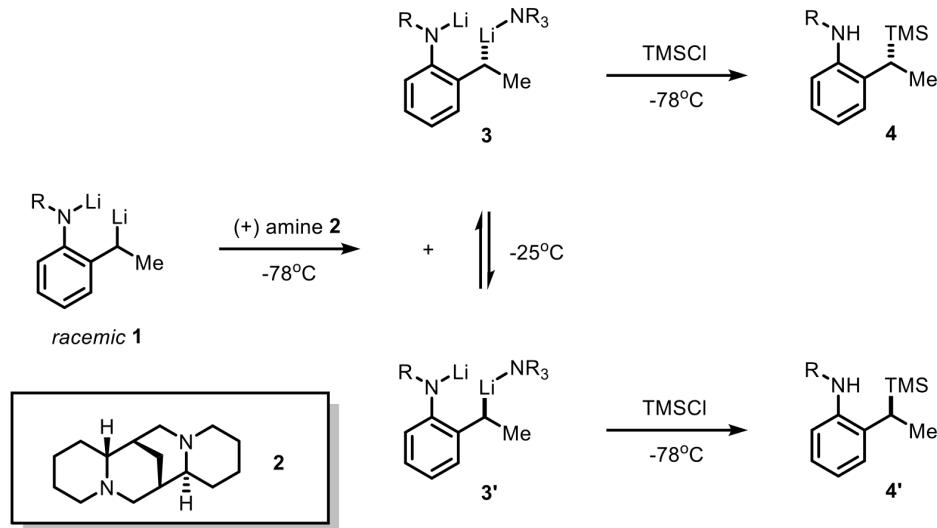


Due to the existence of a stable intermediate, this reaction can have a negative ΔH^\ddagger . □

- d) The mechanism of this reaction is known to be the same in toluene and 1,2-dichloroethane. Based on your answers from part (a) and your energy diagram from part (c), explain how the solvent can make a difference in observed ΔH^\ddagger .

Answer. The solvent can affect the stability of the intermediate and the height of the barrier between intermediate I and the product P. Relatively polar 1,2-dichloroethane is more likely to stabilize the polar intermediate and the transition state, thereby resulting in a negative activation enthalpy for the overall reaction. \square

4. Beak has reported an example of ‘dynamic thermodynamic resolution’ in the asymmetric silylation of benzylic carbanions. In this work, a racemic mixture of dianion **1** is ligated with 1 equivalent of enantiopure amine **2** at -78°C to form equal amounts of two new diastereomeric amine-lithium complexes (**3** and **3'**) that have unequal energy. Although the C–Li stereocenter in **3** and **3'** is configurationally stable at -78°C , upon warming to -25°C , these two anions readily equilibrate. Upon cooling back to -78°C , these anions both react stereospecifically with trimethylsilyl chloride (TMSCl) to form enantiomeric products **4** and **4'**. Use this description and the data provided below to answer the following questions. (Equivalents of TMSCl are with respect to **1**).



reaction	warm to -25°C ?	equiv. TMSCl	4 : 4'
1	No	2.1	50 : 50
2	No	0.1	91 : 9
3	Yes	2.1	92 : 8
4	Yes	0.1	99 : 1
5	Yes	0.5	98 : 2

a) Calculate ΔG° for **3** and **3'** at -25°C .

Answer. Reaction 3 has excess TMSCl, so we get quantitative conversion of **3** to **4** and **3'** to **4'**. Thus, the equilibrium ratio of **3** to **3'** is 92 : 8! It follows that

$$K_{\text{eq}} = \frac{8}{92}$$

and hence

$$\begin{aligned} \Delta G^{\circ} &= -RT \ln K_{\text{eq}} \\ &= -\left(1.9872 \times 10^{-3} \frac{\text{kcal}}{\text{mol K}}\right)(248 \text{ K}) \ln\left(\frac{8}{92}\right) \end{aligned}$$

$$\boxed{\Delta G^{\circ} = 1.2 \text{ kcal/mol}}$$

□

- b) Calculate $\Delta\Delta G^\ddagger$, for the reactions of **3** and **3'** with TMSCl at -78°C .

Answer. In reality, the kinetics of the reactions of **3** and **3'** with TMSCl are governed by the following system of coupled nonlinear ordinary differential equations.

$$-\frac{d[3]}{dt} = k_{34}[3][\text{TMSCl}] \quad -\frac{d[3']}{dt} = k_{3'4'}[3'][\text{TMSCl}]$$

There is no analytical solution to these rate laws. However, under *low* conversion from equal amounts of starting materials, the product ratio is *approximately* equal to the k ratio since we're *closer* to observing initial rates:

$$\frac{k_{34}}{k_{3'4'}} \approx \frac{[4]}{[4']}$$

Thus, using Reaction 2 as our proxy for low conversion with equal amounts of **3** and **3'**, we have

$$\begin{aligned}\Delta\Delta G^\ddagger &= -RT \ln\left(\frac{k_{34}}{k_{3'4'}}\right) \\ &= -RT \ln\left(\frac{[4]}{[4']}\right) \\ &= -\left(1.9872 \times 10^{-3} \frac{\text{kcal}}{\text{mol K}}\right) (195 \text{ K}) \ln\left(\frac{91}{9}\right)\end{aligned}$$

$$\boxed{\Delta\Delta G^\ddagger = -0.9 \text{ kcal/mol}}$$

□

- c) If one first added 0.5 equiv. of TMSCl to an equilibrated mixture of **3** and **3'**, and then subsequently added 2 equiv. of triethylsilyl chloride (TESCl), what would be the enantiomeric ratio of the TES-containing products? What would the ratio of TES-containing products be if one first warmed the reaction to -25°C before adding the 2 equiv. of TESCl?

Answer. We'll take this one question at a time.

First question: Per Reaction 5, adding 0.5 eq. of TMSCl to an equilibrated mixture of **3** and **3'** yields a $98 : 2$ ratio of **4** and **4'**. Additionally, the TMSCl will be consumed quantitatively by hypothesis, we'll have a net 0.5 eq. of **4** and **4'**, divided up into 0.49 eq. **4** and 0.01 eq. **4'** (per the $98 : 2$ ratio). Assuming that we had 0.92 eq. **3** and 0.08 eq. **3'** before adding the TMSCl (per the post-equilibration ratio discussed in part a), this means that we have a remaining $0.92 - 0.49 = 0.43$ eq. **3** and $0.08 - 0.01 = 0.07$ eq. **3'**. Adding the 2 eq. TESCl will then quantitatively convert the remaining **3** and **3'** into analogous TES-containing products, which we may call **5** and **5'**, respectively. Thus, after the TESCl addition, we will have 0.43 eq. **5** and 0.07 eq. **5'**, meaning that the net enantiomeric ratio is $86 : 14$.

Second question: As in the first part, the beginning several steps would leave us with 0.43 eq. **3** and 0.07 eq. **3'** prior to warming. Warming would then reestablish the equilibrium with $K_{\text{eq}} = 8/92$, giving us 0.46 eq. **3** and 0.04 eq. **3'**. Then adding the 2 eq. TESCl would once again yield quantitative conversion to 0.46 eq. **5** and 0.04 eq. **5'**, affording the thermodynamic enantiomeric ratio of $92 : 8$. □

- d) Derive expressions to predict the ratio of **4** and **4'** at both very low conversion (< 1%) and at very high conversion (> 99%) from an equilibrated mixture of **3** and **3'**. Which elementary step(s) is selectivity-determining in each regime?

Answer. At very low conversion, we get almost instantaneous consumption of the TMSCl in approximate correspondence with the initial rates of the two reactions. Thus, from parts (a) and (b), the rates of conversion are

$$\frac{d[4]}{dt} = 91[92][\text{TMSCl}] \quad \frac{d[4']}{dt} = 9[8][\text{TMSCl}]$$

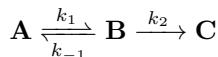
Therefore, the product ratio is $91 \cdot 92 = 8372$ to $9 \cdot 8 = 72$, or approximately $99.1 : 0.9$. This is consistent with the principle of multiplying selectivities. Here, both elementary steps are selectivity-determining.

At very high conversions, almost all TMSCl is consumed and the product ratio reports out the starting material ratio. Thus, like in part (a), we will obtain a 92 : 8 ratio of products. Here, the thermodynamic equilibration is the selectivity-determining step. \square

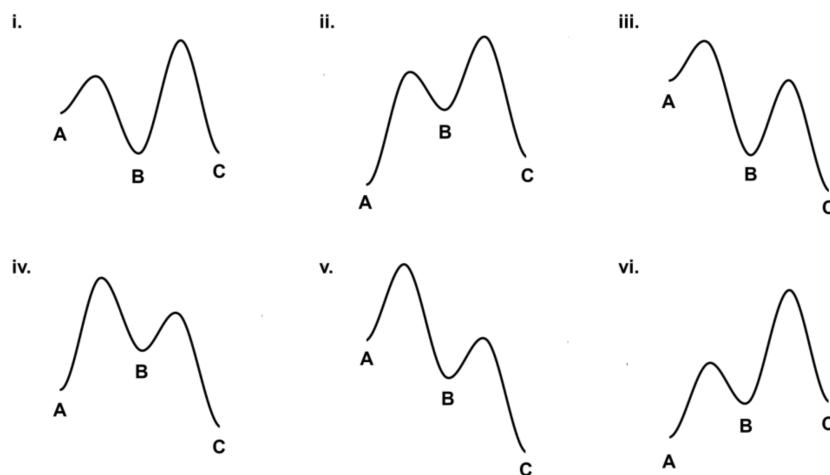
4 Isotope Effects and Kinetics

11/26: The questions pertain to the material covered from Thermodynamic Isotope Effects (Nov 5) to Kinetic Rate Laws (Nov 14).

- The following schematic illustrates the six possible kinetic scenarios for the reaction



of **A** to **C** via **B**.



- In which of these scenarios would the steady-state approximation *not* be valid? Provide a brief explanation for your answers.

Answer. The steady-state approximation would not be valid in Scenarios **i** and **iii**.

i: The initial equilibrium between **A** and **B** is exergonic, and there is a significant barrier before conversion to **C**. Symbolically, $k_1 \gg k_{-1} \gg k_2$. Thus, most of the substrate will exist as **B**. Since $[B] \gg [A]$, the steady-state approximation does not hold.

iii: Again, it is easier for **A** to become **B** than for **B** to become **C**, so most of the substrate will sit as the intermediate.

Notes: If **A** is more stable than **B**, then the SSA is valid; the converse is not necessarily true. □

- In which of these scenarios would the quasi-equilibrium assumption *not* be valid? Provide a brief explanation for your answers.

Answer. The quasi-equilibrium assumption would not be valid in Scenarios **iii**, **iv**, and **v**. The quasi-equilibrium assumption is only valid when $k_{-1} > k_2$. □

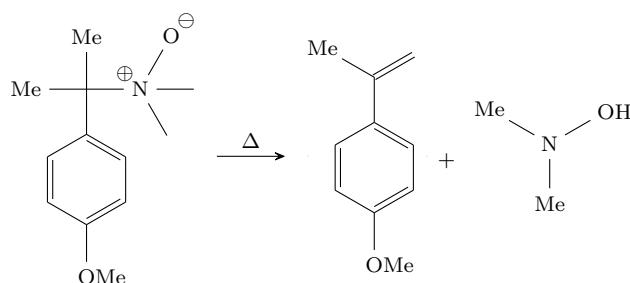
- Consider a situation where **A** is isotopically labeled. If isotopic substitution affects only the rate of conversion of **B** to **C** (and not from **A** to **B**), in which scenarios might you expect to observe an independent rate kinetic isotope effect (KIE)? Please explain.

Answer. Under these assumptions, a KIE would be observed when the second step is rate-determining. Recall that the rate-determining step is the step that has the largest energy difference relative either to the starting material or to any previous, lower energy intermediate on the diagram. Thus, we might expect to observe a KIE in Scenarios **i**, **ii**, **iii**, and **vi**. □

- In which scenarios might you expect to observe an independent rate KIE if isotopic substitution affects only the step involving formation of **B** from **A** (and not from **B** to **C**)?

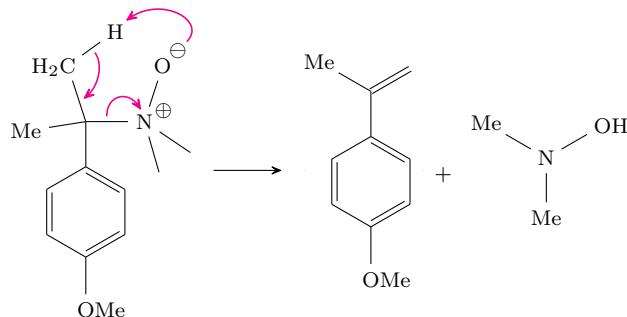
Answer. When the first step is rate-determining, we'll definitely see a KIE. But even when it is not, KIEs will affect $[B]$, altering the rate of the RDS! Thus, all scenarios display KIEs. Answers to all questions in Raines and Hansen (1988). □

2. Consider the following reaction.

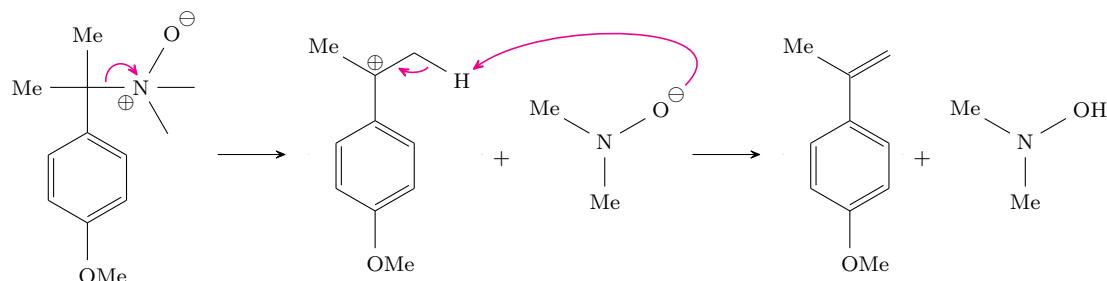


- a) The mechanism for this reaction could proceed via a concerted pathway or a stepwise pathway. Provide arrow-pushing mechanisms for both processes.

Answer. Concerted: This is an E_i mechanism!



Stepwise: This is an E₁-type mechanism!



□

- b) When the two benzylic methyl groups were deuterated, kinetic isotope effects (KIEs) of 5 and 1.2 were measured in toluene and DMF respectively. Suggest a possible explanation for the observed KIEs.

Answer. A large, likely primary KIE of 5 suggests that C–H/D bond cleavage is part of the RDS. Since the RDS of the concerted mechanism (the only step) involves C–H/D bond cleavage and the RDS of the stepwise mechanism (likely the first step, as is typical of E₁-type mechanisms) does not involve C–H/D bond cleavage, the concerted mechanism is likely active in toluene.

A small, likely secondary KIE of 1.2 suggests that C–H/D bond cleavage is *not* part of the RDS. Thus, for analogous reasons to the above, the stepwise E₁-type mechanism is likely active in DMF.

□

- c) When the reaction was run at two different temperatures and in two different solvents, the following rate data were obtained. Compare the activation enthalpy (ΔH^\ddagger) and activation entropy (ΔS^\ddagger) of the reactions in toluene and in DMF. Suggest a possible explanation for the observed differences.

T (°C)	k_{rel} in toluene	k_{rel} in DMF
60	1	10
110	50	500,000

Answer. Although it is not possible to obtain absolute values (e.g., in kcal mol^{-1}) for ΔH^\ddagger and ΔS^\ddagger from this data, a modified Eyring plot can compare the magnitudes of these quantities between the two reactions. For toluene, the line through

$$\left(\frac{1}{273 + 60}, \ln(1) \right) \quad \left(\frac{1}{273 + 110}, \ln(50) \right)$$

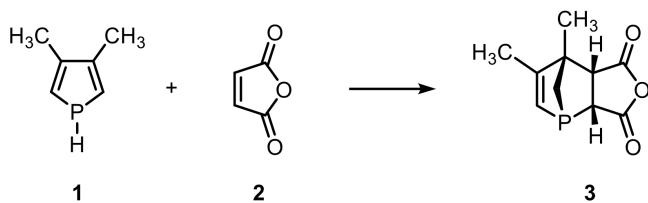
has slope $m = -9979$ and y -intercept $b = 29.97$, so $\Delta H_{\text{rel}}^\ddagger = 19.74$ and $\Delta S_{\text{rel}}^\ddagger = 0.0593$. For DMF, the line through

$$\left(\frac{1}{273 + 60}, \ln(10) \right) \quad \left(\frac{1}{273 + 110}, \ln(500\,000) \right)$$

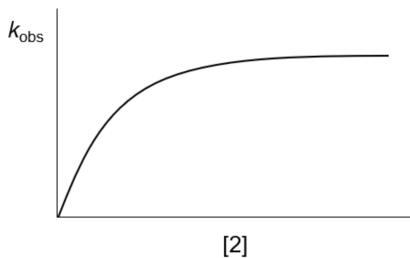
has slope $m = -27600$ and y -intercept $b = 85.18$, so $\Delta H_{\text{rel}}^\ddagger = 54.6$ and $\Delta S_{\text{rel}}^\ddagger = 0.169$.

It follows that the reaction in DMF — which proceeds via the stepwise mechanism, per part (b) — has both a higher enthalpy and entropy of activation. It makes sense that it should have a higher enthalpy of activation since the RDS involves the formation of a high-energy carbocation intermediate. It also makes sense that it should have a higher entropy of activation because the introduction of charged species into a polar aprotic solvent will disrupt the random bonding of the solvent to itself and introduce highly ordered ion cages. \square

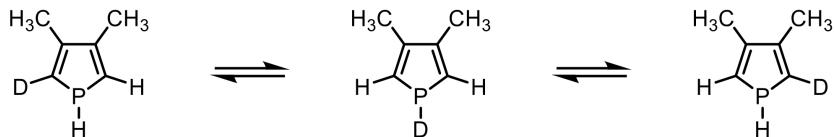
3. In nonpolar solvents, compound **1** reacts thermally with **2** to give only *endo* **3**.



Using small amounts of **1** and ‘flooding’ with **2**, it has been established that the rate is pseudo-first-order in **[1]**. Measuring the pseudo-first-order rate constant k_{obs} at several different concentrations of excess **2** gives a plot of the type shown below.

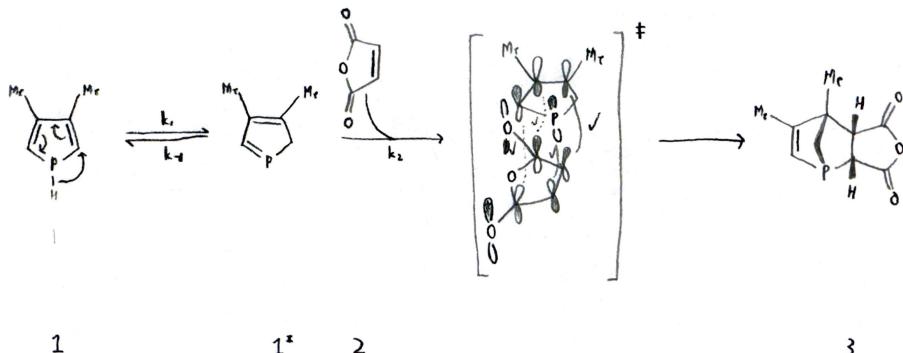


Compound **1**, deuterated at phosphorus, undergoes exchange of D with both α -hydrogens, as shown below. At low concentrations of **2**, the H/D exchange rate is rapid compared to the rate of formation of **3**. At ‘saturating’ concentrations of **2**, the formation of **3** occurs faster than H/D exchange.



- a) Write a full mechanism and a rate law for the formation of **3** that is consistent with these observations.

Answer. A full mechanism consistent with these observations is



A rate law consistent with these observations is

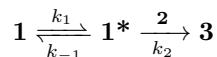
$$\text{rate} = \frac{k_1 k_2 [1][2]}{k_{-1} + k_2 [2]}$$

□

- b) Explain how your mechanism accounts for the labeling and kinetic behavior.

Answer. We begin by developing a plausible arrow-pushing mechanism for the overall indicated transformation. Nonpolar solvents, thermal reactivity, a starting material (**2**) with two strong EWGs, and *endo*-selectivity suggests that **3** was ultimately formed by a [4 + 2] cycloaddition. Taking the six-membered ring in **3** to be a full retrone for a [4 + 2] cycloaddition, we can predict **1*** and **2** as starting materials. Indeed, **1*** and **2** would react in the forward direction via the indicated transition state, with bonds being formed between the HOMO of **1*** and the full LUMO of **2**; *endo*-selectivity is secured by the two secondary orbital interactions indicated with dashed lines. This just leaves the question of where **1*** could have come from. One possible option is from **1** via a suprafacial [1, 5]-sigmatropic H-atom shift. Such pathways are very common for such doubly unsaturated systems, so this is a reasonable hypothesis.

Let's now see why this plausible mechanism is defensible based on the given data, and in the process derive the above rate law. To begin, a simplified chemical equation is



Based on this equation, we would predict that

$$\text{rate} = \frac{d[\mathbf{3}]}{dt} = k_2[\mathbf{1}^*][\mathbf{2}]$$

To (analytically) express $[\mathbf{1}^*]$ in terms of $[\mathbf{1}]$, we may choose between four possible simplifying assumptions:

- The steady-state approximation.
- The steady-state approximation, accounting for $[\mathbf{1}]_T$.
- The quasi-equilibrium assumption.
- The quasi-equilibrium assumption, accounting for $[\mathbf{1}]_T$.

Using these assumptions, we may derive the following four rate laws, respectively.

$$\text{rate} = \frac{k_1 k_2 [\mathbf{1}][\mathbf{2}]}{k_{-1} + k_2 [\mathbf{2}]} \quad \text{rate} = \frac{k_1 k_2 [\mathbf{1}]_T [\mathbf{2}]}{k_1 + k_{-1} + k_2 [\mathbf{2}]} \quad \text{rate} = \frac{k_1 k_2}{k_{-1}} [\mathbf{1}][\mathbf{2}] \quad \text{rate} = \frac{k_1 k_2}{k_1 + k_{-1}} [\mathbf{1}][\mathbf{2}]$$

Both equations derived under the quasi-equilibrium assumption fail to account for the saturation kinetics on display in the k_{obs} vs. $[\mathbf{2}]$ plot, so we can rule them out. Thus, this reaction must occur in a regime subject to the steady-state approximation. It follows that $k_{-1} \gg k_1$, so we may additionally neglect the k_1 term in the denominator of the fourth option, leaving the indicated rate law as our choice.

Additionally, observe that in the limiting case of ‘flooding’ with **2**, $k_2[\mathbf{2}] \gg k_{-1}$. This allows the rate law to collapse to

$$\text{rate} = k_1[\mathbf{1}] = k_{\text{obs}}[\mathbf{1}]$$

corresponding to the observation of that the reaction is pseudo-first-order in **1** under these conditions!

In the case of low concentrations of **2**, the rate law also collapses to an expression that is first-order in $[\mathbf{2}]$, consistent with the plot.

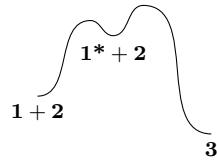
Furthermore, the proposed reversible first step would account for the hydrogen-deuterium exchange at the symmetric α -carbons (even in the absence of **2**): D could migrate from the phosphorus center to either α -carbon, and then either D or H could migrate back.

The final observation regarding the relative rates of H/D exchange vs. the rate of formation of **3** will be useful in part (c). □

c) Draw reaction coordinate energy diagrams at the limiting cases where [2] is...

- i) Very low;

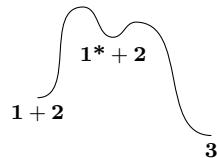
Answer.



Since this reaction obeys the steady-state approximation as discussed in part (b), not much $\mathbf{1}^*$ is ever formed. Thus, $\mathbf{1}^* + \mathbf{2}$ should always be higher in energy than $\mathbf{1} + \mathbf{2}$. Additionally, since the reaction proceeds, it should always be exergonic. Finally, the difference in the heights of the transition states comes from the data that H/D exchange is faster than formation of $\mathbf{3}$ at low concentrations of $\mathbf{2}$; this observation implies a lower barrier for $\mathbf{1}^* + \mathbf{2}$ to return to the reactants than proceed on to the products. \square

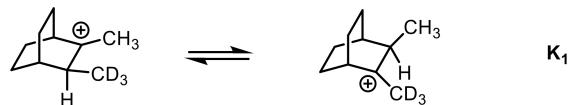
- ii) Very high.

Answer.



The analysis is identical to the part (c.i), except that conversion to the products now occurs faster, so its barrier should be lower. \square

4. a) Estimate the magnitudes of the equilibrium constants (K_1 , K_2) for the following reactions. Provide explanations.



Answer. C–D bonds have a slightly greater BDE than C–H bonds. Thus, they hold onto their electrons more tightly and are less likely to participate in stabilizing interactions like hyperconjugation. Essentially, carbocations subject to $\sigma_{\text{CH}} \rightarrow p_{\text{C}}$ hyperconjugation will be more stable than those subject to $\sigma_{\text{CD}} \rightarrow p_{\text{C}}$ hyperconjugation, all else being equal. Thus, we should have

$$K_1 < 1$$

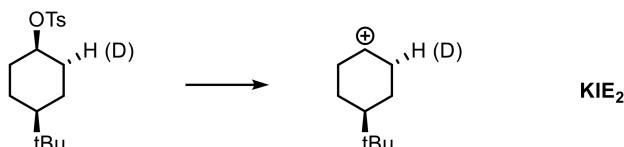
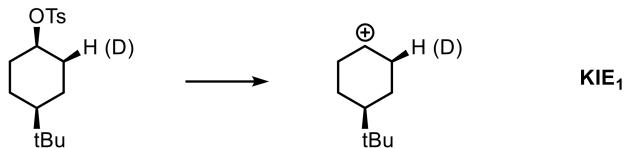
Note that K_1 will likely be only slightly greater than one: When we compared diaxial interactions between methyl groups and perdeuterated methyl groups in class, K_{eq} was 1.042.

For K_2 , the σ_{CD} -orbital is orthogonal to the carbocation's p_{C} orbital, so it cannot stabilize it anyway. Thus, we should have

$$K_2 \approx 1$$

□

- b) Estimate the magnitudes of KIE_1 and KIE_2 for the following solvolysis reactions. Provide explanations.



Answer. The same effects at play in part (a) are also in effect here, except that the type of hyperconjugation is now anomeric $\sigma_{\text{C}-\text{H/D}} \rightarrow \sigma_{\text{C}-\text{O}}^*$ donation. A lack of orbital alignment for the top reaction means that

$$\text{KIE}_1 \approx 1$$

Orbital alignment in the bottom case will predict a small normal secondary KIE:

$$\text{KIE}_2 \in (1, 1.5)$$

□

References

- Anslyn, E. V., & Dougherty, D. A. (2006). *Modern physical organic chemistry*. University Science Books.
- Raines, R. T., & Hansen, D. E. (1988). An intuitive approach to steady state kinetics. *Journal of Chemical Education*, 65(9), 757–759. <https://doi.org/10.1021/ed065p757>