

3 Noncovalent Interactions and Thermodynamics

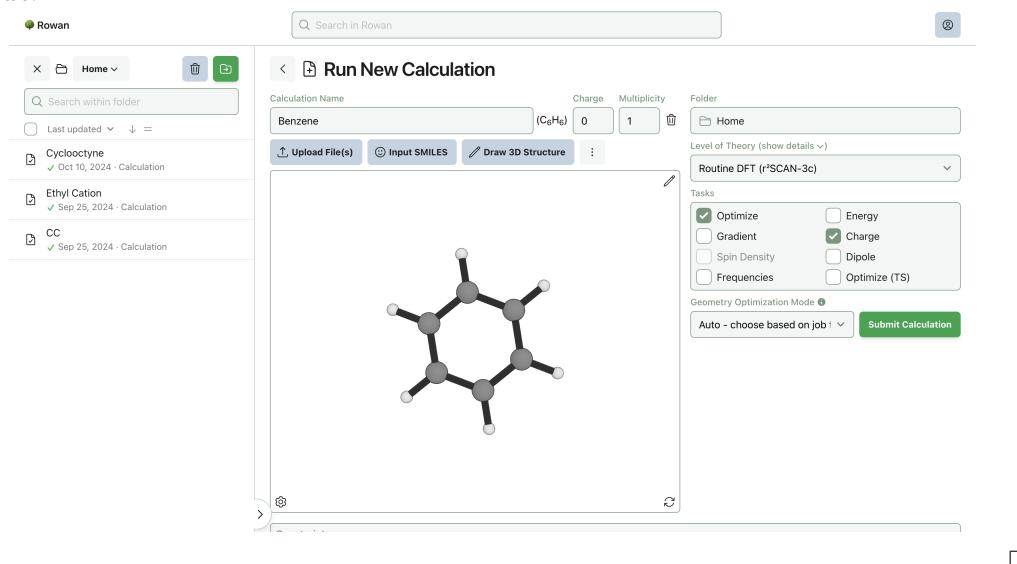
11/14: The questions pertain to the material covered from Noncovalent Interactions (Oct 24) to Isotope Effects (Nov 5).

- 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.

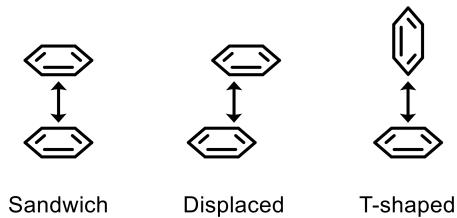
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C -1.08186402 -0.87624412 0.02492904
C -1.29957346 0.49892716 0.02069361
C -0.21782322 1.37512844 -0.00423311
H 1.92529173 1.55932611 -0.04436360
H 2.31283908 -0.88800382 -0.03682784
H 0.38774005 -2.44726076 0.00753188
H -1.92529254 -1.55932713 0.04436366
H -2.31283985 0.88800436 0.03682783
H -0.38773950 2.44726073 -0.00753189
```

□

- How are the charges distributed on the molecule?

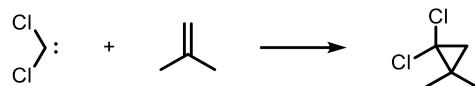
Answer. The Mulliken partial charges are all concentrated symmetrically on the carbon atoms, -0.150 on each carbon and +0.150 on each hydrogen. □

- 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). □

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).

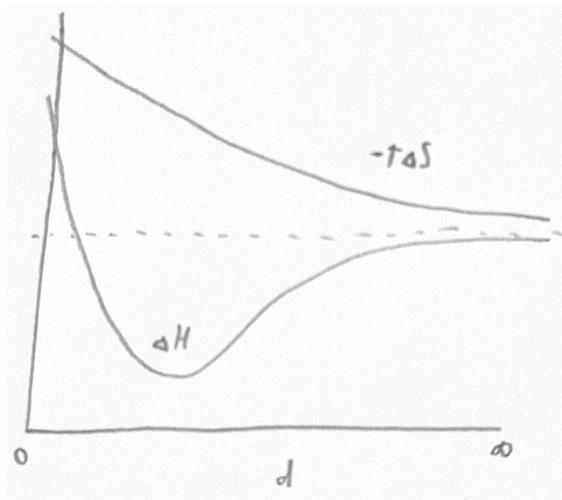


- a) Consider the reverse reaction. Conduct a thought experiment in which we gradually pull dichlorocarbene away from isobutylene. How would ΔH vary with distance? How would ΔS vary with distance? Draw an energy diagram depicting both ΔH and $-T\Delta S$ as functions of distance on a single plot. Assume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

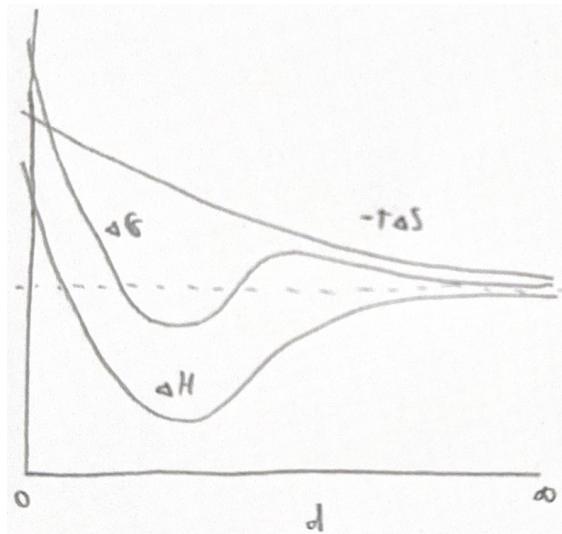
$-T\Delta S$ increases as distance decreases, accelerating as the species get closer together. This is because the entropy drops as we go from two molecules to one, probably by close to 30 e.u.. Essentially, we are forming a highly-ordered single-molecule product that is much less entropically favorable.



□

- 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).

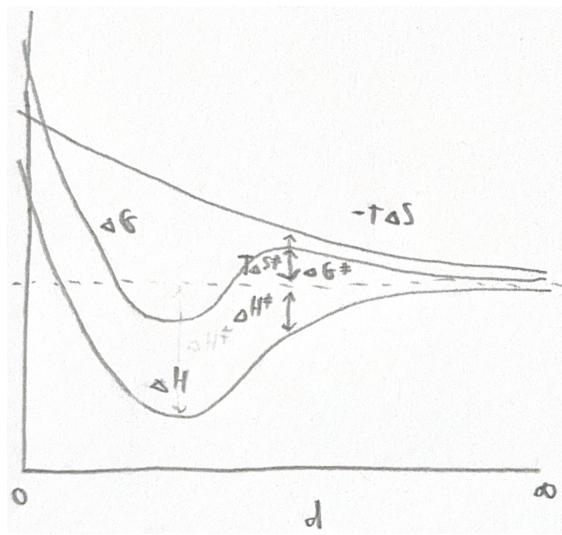
Answer. As the molecules get farther apart, ΔG would be negative at first (due to ΔH) and then positive later (due to ΔS).



□

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

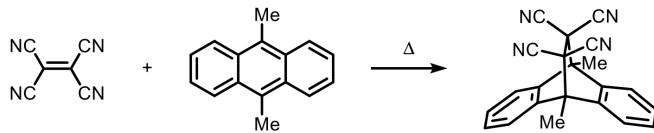
Answer.



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

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

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

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

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

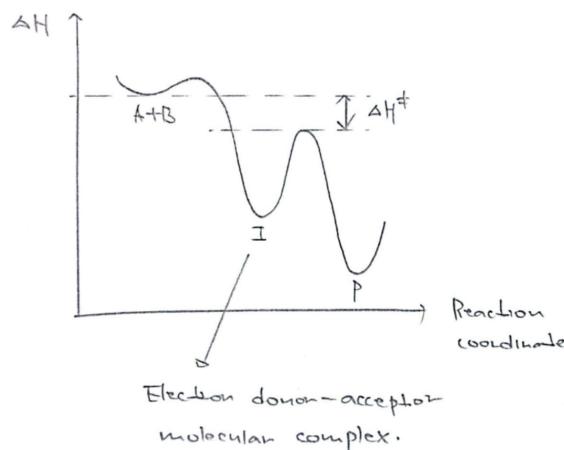
□

- 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 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.

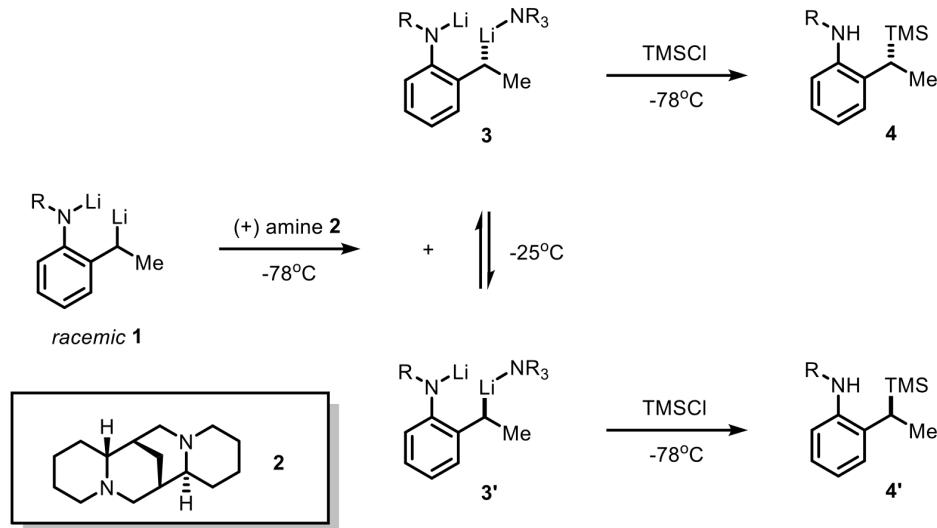


Due to the existence of a stable intermediate, this reaction can have a negative ΔH^\ddagger . □

- 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