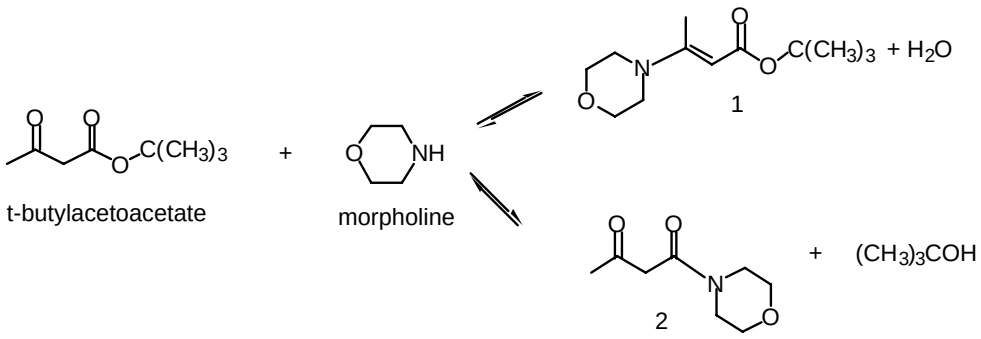
Reaction of Morpholine with t-Butyl Acetoacetate:
Kinetic vs. Thermodynamic Control
adapted from *J. Chem. Ed*.

Objectives:
1. To use molecular modeling for identification of the thermodynamically controlled reaction product
2. To demonstrate experimentally kinetic versus thermodynamic control in the reaction of morpholine and t-butyl acetoacetate (for background information see Ege pp 865-868)
3. To analyze products using a combination of characterization methods (NMR and GC/MS)

You will be completing the molecular modeling portion of the experiment as well as starting the synthesis in the first week. In the second week, the products will be isolated and analyzed.

Overview:
The reaction of morpholine with t-butyl acetoacetate in a one-to-one molar ratio results in one of two products, **enamine ester 1** or **ketoamide 2**. (You will not be able to look up chemical properties of **1** and **2**.)



In these reactions, a competition takes place where two functional groups on a single molecule are competing for a single reagent. You will be performing the above reactions and analyzing the products produced under two sets of conditions, one favoring kinetic control and one favoring thermodynamic control. Using information gathered by molecular modeling, NMR, and GC/MS, you will be able to determine which reaction is the kinetic and which is the thermodynamically controlled process.

Procedure:
Molecular Modeling

Theoretical semi-empirical molecular modeling calculations can be used in order to determine which reaction is thermodynamically favored. You should calculate the AM1 energy of the following compounds and report the results in a table in your notebook: water, t-butanol, morpholine, t-butylacetoacetate, (E)-enamine **1**, and ketoamide **2**.

1. From the Desktop menu choose Spartan '04.
2. Before performing a calculation, you must build a molecule then save it. Click on **File** and choose **New**. This opens the building tools so can construct the molecule. The basic building tools are shown on the right side of the screen.
3. Build the molecule of interest. The following instructions will make this easier.
   The following mouse commands are useful as you are building in Spartan:

   Left mouse: rotate molecule
   Right mouse: translate molecule
   Shift-left mouse: rotate molecule in plane of screen
   Shift-right mouse: enlarge/shrink molecule
   Alt-left mouse (when bond is highlighted): rotate torsion angle
   Alt-right mouse (when bond is highlighted): stretch/shrink bond length

4. Before performing a semi-empirical calculation, you can "clean-up" the molecule you built using a quick minimization. Click the **Minimize** button at the top of the screen. (*E with down arrow*).
5. Save the molecule. Under the **File** menu, choose **Save As** and save the file in the folder **Chem302L** on the desktop. Name the file with your initials and a sequential number e.g. aaa1.
6. Choose **Semi-Empirical** under the **Setup**-**Calculations** menu. The Setup Semi-Empirical Dialog box appears; set the tasks as follows:

   Calculate: Equilibrium Geometry (pull down menu) **Total Charge:** 0
   with: Semiempirical AM1 **Multiplicity:** singlet
   Start from: initial geometry
   Options: leave this box blank

7. Click the submit button. When the job is finished and you click OK, the molecule's structure is updated. The calculated energy can be found under **Display**, then **Properties**. Record this energy.

Synthesis

Reaction Conditions A.

1. Place a mixture consisting of a 0.05 mol morpholine and 0.05 mol of t-butyl acetoacetate into a beaker cooled with ice water.
2. Place two molecular sieve pellets into the beaker.
3. Cover the beaker with a watch glass and *place it in your drawer for study next week*. Be sure to label this beaker.

Reaction Conditions B.

4. Place 0.05 mol of t-butylacetoacetate into a 25 mL round bottom flask equipped with a stirring bar and a distillation adapter leading to a condenser. [This is a typical distillation setup. Remind yourself what this setup should looks like (refer to Figure 5.5 on p 71 of the lab textbook). The only difference is that you will be heating the RBF using a sand bath (a glass container with sand in it) on top of a hot plate in place of a heating mantle. The hot plate will be the source of heat, and the sand will evenly distribute the heat to the RBF.]
5. Heat the flask in sand bath to approximately 165°C.
6. Add an equimolar amount of morpholine while maintaining the temperature (add approximately 0.5 mL every five minutes). During the slow addition of morpholine, some liquid distills over. After the morpholine addition is complete, the liquid continues to distill.
7. When the distillation is complete, the reaction mixture should cool to room temperature.
8. After cooling, transfer the product mixture to a beaker, cover it with a watch glass, *and place it in your drawer until next week.* Be sure to label this beaker.

Isolation and Analysis

1. Remove the molecular sieves from the crystals that should have formed from the room-temperature reaction (A). Isolate the crystals by vacuum filtration and wash with a small amount of ether and let dry.
2. Isolate the crystals from the second reaction in the same way (B).
3. Obtain final masses for each product.
4. Obtain ^{1}H NMR, ^{13}C NMR, and GC/MS spectra for each product.

Questions to start thinking about

What does the computational data tell you?
Which product was formed under condition A? Which product was formed under condition B? What data confirms the structure assignment?
What is the liquid that distills over during the reaction (B)?