Reaction of Morpholine with t-Butyl Acetoacetate: A Study in Kinetic vs Thermodynamic Control, Product Identification, and Molecular Modeling


Note: This is from Chem 36H. You do not need to do Prelab & PostLab exercises as such but you should discuss the ideas therein. Molecular modeling is optional.

Introduction

This experiment demonstrates the following principles and techniques: (i) kinetic versus thermodynamic control of a reaction, (ii) methods to be used and pitfalls to be avoided in identification of reaction products, (iii) use of molecular modeling for identification of the thermodynamically controlled reaction product.

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 (eq 1).

\[
\begin{aligned}
\text{enamine ester} & \quad + \quad \text{H}_2\text{O} \\
\text{CH}_3\text{OC(\text{CH}_3)_3} & \quad + \quad \text{O} \quad \text{NH} \\
\text{ketoamide} & \quad + \quad \text{HO}\text{C(\text{CH}_3)_3}
\end{aligned}
\]

The reaction of a secondary amine with an acetoacetic ester to form an enaminoester is well known (1–3). The t-butyl ester was used in our experiment instead of the more common ethyl ester because t-butyl morpholine enamine 1 (4) is a solid that melts well above room temperature. The corresponding ethyl enaminoester possesses a melting point very near to room temperature (5) and is therefore difficult to crystallize. The reaction of a secondary amine with an acetoacetic ester to form a ketoamide has been reported (5, 6). It has been demonstrated that the enamino-ester is the kinetically controlled product and the ketoamide is the thermodynamically controlled product (7).

These reactions provide the basis for an experiment in which the competition between thermodynamic control and kinetic control takes place between two functional groups on a single molecule competing for a single reagent. This is in contrast to a traditional experiment used to demonstrate this principle, which is found in many organic laboratory manuals (8). In that experiment two different molecules (cyclohexanone and 2-furaldehyde) compete for a single reagent (semicarbazide).

Molecular modeling will be used to calculate which of the two products is the more thermodynamically stable. The reaction will be run at lower temperatures whereby the kinetic product is formed and at high temperature at which the more thermodynamically stable product is formed.

Prelaboratory Exercise

The enamino-ester 1 is shown in its E form. Draw the structure of the Z form. Build these two forms in Spartan and calculate their energies by a semi-empirical method, AM-1.

The ketoamide is shown in its keto- form. Draw the enol form. Build these two forms in Spartan and calculate their energies by a semi-empirical method, AM-1.
Both the kinetic and thermodynamic products from the low and high temperature reactions below melt in the 69-72°C range. Using melting point only, how can you determine that these two products are indeed two different compounds?

Cautions

Morpholine has an unpleasant odor. Run all reactions under the hood.

Experimental Procedure

Reaction at room temperature:

Place a mixture consisting of 10 mmol each of morpholine and t-butyl acetoacetate into a reaction tube cooled with ice water. Put two molecular sieve pellets (2A, 4–8 mesh) into the tube, cork loosely and let stand in your locker until the following laboratory period, when it will be observed that crystals have formed. In the following laboratory period, 1 mL of ether is added to the reaction tube which is cooled and ice and the ether removed by pipet filtration. The crystals are washed with an additional 0.5 mL of cold ether, dried, and a melting point taken.

Reaction at high temperature:

The ester t-butyl acetoacetate (20 mmol) is placed in a 5-ml short-neck round-bottom flask tube equipped with a 1/2” magnetic stirring bar and a distillation head a septum on top in place of a thermometer. The flask is heated in a small beaker of diocetyl phthalate heated to 165-175°C on a combination stirrer-hotplate (obtainable at stockroom). An equimolar amount of morpholine is slowly added by syringe injection through the septum while the temperature is maintained between 165 and 175°C. During the slow addition of morpholine, some liquid (t-butanol) distills over. After the morpholine addition is complete, the liquid continues to distill. When the distillation of the lower-boiling liquid (t-butanol) is stops, the reaction mixture is allowed to cool and is then transferred to a small beaker. The beaker is placed in your locker and covered with a larger beaker. Colorless crystals will have formed in the beaker by the next laboratory period. These are isolated by vacuum filtration, washed with ether, and allowed to dry. The keto amide may be recrystallized from toluene, but it normally isn’t necessary.

Take melting points of both the low and high temperature reaction products and a mixed melting point of the two products. Analyze both by GC-MS and interpret the mass spectrum so as to verify the correct structure. Both proton and carbon magnetic resonance spectra of each set of crystals show the room-temperature crystals to be enaminoester 1 and the high-temperature crystals to be ketoamide 2. DEPT spectra help to confirm the carbon spectral assignments. Use of carbon NMR prediction software such as Softshell’s C-13 NMR Module is very useful here. You can determine the amount of enol form of ketoamide 2 present in deuterochloroform by integrating the proton magnetic resonance signals of the amide’s terminal methyl group signals at 1.95 (enol) and 2.27 (keto) ppm. This should show that there is about 15% of the enol form and 85% of the keto form present in the fairly polar deuterochloroform solvent. The IR spectrum of enaminoester 1 should show bands at 1699 and 1597 cm⁻¹. The IR spectrum of ketoamide 2 should show bands at 1723 and 1640 cm⁻¹.

It is worthwhile to examine these reactions using GC-MS. A very small amount of a solution cooled to ice-bath temperature of a 1:1 molar ratio of morpholine and t-butyl acetoacetate is injected into a GC–MS, and a chromatogram and some mass spectra are obtained. [The GC is programmed from 70 °C to 250 °C at 20°C/min. Analysis of this chromatogram shows about 98% ketoamide 2 and 2% enaminoester 1. The ketoamide has a shorter retention time than the enaminoester, identification of the peaks being obtained from the mass spectra. This chromatogram indicates almost exclusively ketoamide 2 as the product at this low temperature and hence it “appears” to be the kinetically controlled product, which is contrary to the actual fact. This is a good illustration of the possibility (and in this case, the actuality) of reactions taking place on a GC column. Indeed, it has been shown by an “on-column pursuit” experiment that this reaction does take place in a column at 190 °C, with β-keto esters forming ketoamides on the GC column when they are allowed to react with secondary amines (9). You can demonstrate the on-column pursuit technique with this reaction by first injecting the less volatile β-ketoester onto the column and then injecting the more volatile amine to produce a significant β-ketoamide peak.

Molecular Modeling

Determine which reaction is thermodynamically favored (at least in the gas phase) according to theoretical semiempirical molecular modeling calculations. AM-1 calculations using a molecular modeling program such as Spartan show the reaction resulting in the formation of ketoamide 2 to be the favored reaction by about 7.5 kcal/mol; that
is for enaminoester 1, \(-59.240 - 123.018 = -182.258\) kcal/mol, and for ketoamide 2, \(-118.092 - 71.601 = -189.693\) kcal/mol (see Table 1). Ab initio calculations using HF/6-31G* give a similar result of 0.0280572 hartree (ignoring zero-point energies), favoring ketoamide 2. In these calculations the more stable keto form of ketoamide 2 is used, and the more stable \(E\) isomer of enaminoester 1 is used.

Table 1. Energies from Molecular Modeling

<table>
<thead>
<tr>
<th>Compound</th>
<th>Semiempirical AM-1</th>
<th>Ab Initio 6-31 G*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kcal mol-1</td>
<td>Hartrees</td>
</tr>
<tr>
<td>Water</td>
<td>-59.240</td>
<td>-76.0107465</td>
</tr>
<tr>
<td>(t)-butanol</td>
<td>-71.601</td>
<td>-232.1534707</td>
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<tr>
<td>Morpholine</td>
<td>-49.346</td>
<td>-285.9977181</td>
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<tr>
<td>(t)-butyl acetoacetate</td>
<td>-142.548</td>
<td>-535.7136091</td>
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<tr>
<td>(Z)-enaminoester 1</td>
<td>-121.131</td>
<td>-745.6603501</td>
</tr>
<tr>
<td>(E)-Enamine 1</td>
<td>-123.018</td>
<td>-745.6688848</td>
</tr>
<tr>
<td>Ketoamide 2</td>
<td>-118.092</td>
<td>-589.5542168</td>
</tr>
<tr>
<td>(Z)-Enolamide 2</td>
<td>-116.511</td>
<td>-589.5481199</td>
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Literature Cited