Kinetic vs. Thermodynamic Control in the Dehydration of 2-Methylcyclopentanol

A Two-Part Laboratory Experiment Utilizing the Grignard Reaction and GC-MS[1]

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The concept of kinetic versus thermodynamic control is a common theme in organic chemistry. In the introductory organic chemistry classroom, it is often used to explain the products obtained in dehydration reactions, additions to conjugated olefins, and enolate formation. However, while the concept is firmly entrenched in the lecture curriculum, applications of kinetic versus thermodynamic control in the laboratory are less common (*1–3*)—though such experiments can be found in the primary literature (*4–11*). The following describes a two-part laboratory experiment involving a Grignard reaction to form an unsymmetrical cyclopentanol and a subsequent acid-catalyzed dehydration to form the more thermodynamically stable alkene.

The reaction of phenylmagnesium bromide with 2-methylcyclopentanone (**1**) followed by acidic workup yields the unsymmetrical 2-methyl-1-phenylcyclopentanol (**2**). The acid-catalyzed dehydration of **2** using toluenesulfonic acid initially gives the less substituted alkene (**3**) as the major product. Application of heat to the reaction mixture over a period of two hours reverses the trend, to give the more substituted alkene as the major product (**4**) in 91% relative yield (Fig. 1).

The dehydration reaction is followed by GC-MS. Initially, the peak area of **3**, which elutes first, is larger than that of **4** and constitutes 55% of the two alkene products. However, as the reaction mixture is heated, the peak area of **3** decreases relative to that of **4** until **4** becomes the major product. This illustrates the thermodynamic stability of **4** over **3**. This stability is also predicted using computational methods. Calculations at the ab initio 6-31G* level of theory determine **4** to be 1.442 kcal/mol lower in energy than **3**, and correctly predict the final ratios of products.

The experiment is designed to cover two 4-hour laboratory sections and is intended to illustrate the following concepts and techniques:

1. the Grignard reaction
2. the dehydration reaction of a tertiary alcohol
3. the use of gas chromatography to separate a mixture and quantify product yields
4. the use of mass spectrometry to characterize organic compounds
5. the concept of kinetic versus thermodynamic control

Materials And Methods

2-Methylcyclopentanone was obtained from Aldrich (catalog no. 28,843-8). Magnesium turnings (19108-0025), sodium sulfate (19664-0025), toluene (17685-0010), dichloromethane (11346-0025), and sodium bicarbonate (21712-0010) were obtained from ACROS. Anhydrous ether (E138-1), bromobenzene (B253-1), and sulfuric acid (A298-212) were obtained from Fisher Scientific. Toluenesulfonic acid (P 984)
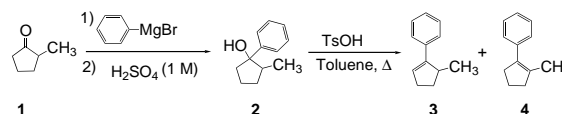
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Figure 1. Formation of the kinetically and thermodynamically favored alkenes **3** and **4** from **1**.

was obtained from Eastman Kodak. Calcium chloride was obtained from J. T. Baker Chemical Co. (1313).

GC-MS analyses were performed on a Hewlett Packard 5890 gas chromatograph coupled to a 5970 series mass selective detector. The column used was a Supelco 2-4026 15-m × 0.25-mm capillary column packed with SPBM-1 (0.25 μm). GC conditions were as follows: injector and detector temp = 200 °C; oven conditions: initial temp = 70 °C; initial time = 1 min, rate = 15°/min, final temp = 200 °C, final time = 1 min. The total time for each run was 10.67 min.

Procedure

The Grignard Reaction:
Preparation of 2-Methyl-1-phenylcyclopentanol

As with any Grignard reaction, care should be taken to assure the use of dry glassware and solvent. A magnetic stir bar, 0.47 g of magnesium turnings, and 15 mL of anhydrous ether are placed in a 100-mL, two-necked round-bottom flask fitted with a reflux condenser and an addition funnel containing 2.0 mL of bromobenzene and 5.0 mL of anhydrous ether. A drying tube filled with calcium chloride is connected to the top of the reflux condenser. The bromobenzene solution is then added dropwise at a rate of 1 drop per second with stirring. The appearance of a cloudy reaction mixture signals the initial reaction of magnesium with the halide. The reaction is refluxed after all the bromobenzene has been added. During this time, a solution of 2.0 mL of 2-methylcyclopentanone in 10 mL of anhydrous ether is placed in the addition funnel. After refluxing for 30 min, the heat source is removed and the ketone solution is added dropwise at a rate of 1 drop per second to the Grignard. The heat given off allows the reaction to continue refluxing on its own and a green solution results. After all the ketone solution is added, the heat source is used to continue the reflux for an additional 15 min. The mixture is then cooled in a warm water bath; additional cooling in an ice bath follows. An ether/ethanol solution is made by mixing 1.5 mL of ethanol and 10 mL of ether. While the reaction mixture is still in the ice bath, the ether/ethanol solution is placed in the addition funnel and added slowly (ca. 1 drop per second) to the reaction mixture. This causes formation of a precipitate of magnesium salts. The resulting solution is greenish yellow. Next, 20 mL of a 1 M sulfuric acid solution is placed in the addition funnel and added dropwise to the reaction mixture (still in the ice bath) to dissolve the magnesium salts. The stir bar is removed, and the contents of the flask

are transferred to a separatory funnel. The lower aqueous layer is removed and extracted twice with 15-mL portions of ether. All three ether layers are combined and dried with anhydrous sodium sulfate. Gravity filtration of the drying agent yields a clear yellow solution. The ether and ethanol are removed using a rotary evaporator (or alternatively via simple distillation) to give a slightly viscous yellow liquid. The crude alcohol product can be analyzed by GC-MS or IR to verify the formation of an alcohol. The product is stored in a sealed vial and saved for the dehydration portion of the experiment.

Kinetic vs. Thermodynamic Control: The Dehydration of 2-Methyl-3-phenyl-3-cyclopentanol

A magnetic stir bar, 0.64 g of the alcohol from the Grignard reaction, 20 mL of toluene, and 0.05 g of toluenesulfonic acid are placed in a 50-mL two-necked flask fitted with a reflux condenser and a ground glass stopper. The flask is placed in a heating basket and the solution is refluxed with stirring. The initial yellow of the solution becomes a deep purple as the reaction proceeds. After 15 min,[2] 4 drops of the reaction mixture are removed via disposable pipet and placed in an microcentrifuge tube containing 0.5 mL of dichloromethane and 0.5 mL of 10% sodium bicarbonate. The reaction solution forms a brown layer at the top of the microcentrifuge tube, giving three layers in total. The microcentrifuge tube is capped and the contents are vigorously shaken. Upon settling, two layers form in the tube: an aqueous layer on top and a clear brown organic layer on the bottom. A GC syringe is used to take a 1-mL sample from the lower dichloromethane layer. This sample is then analyzed by GC-MS. Additional samples are taken from the reaction mixture in a similar manner every 15–20 min for a total of 2 hours. The samples need not be analyzed immediately, since the sodium bicarbonate solution was used to neutralize the toluenesulfonic acid.

Results and Discussion

The GC-MS analysis of the product mixture from the Grignard reaction shows that the alcohol (*2*) is the major product of the reaction (79% yield relative to all products) with a retention time of 5.54 min. Peaks appearing at 4.62 and 4.73 min show that a minor amount of dehydration has already occurred, perhaps during the acid workup. The other by-products are minor as well and do not effect the dehydration reaction.

The toluenesulfonic acid–catalyzed dehydration of **2** initially gives a 55:45 ratio of **3** to **4** (Table 1). Over a period of two hours under reflux, the ratio is converted to 8.8:91. This implies that the less substituted alkene (**3**) is more easily formed, while the tetrasubstituted alkene is more stable and becomes the major product under accelerated equilibrium conditions.

It is interesting to note that computational studies on this system agree very well with experiment. Single point energies[3] of the alkenes, cal-

Table 1. Ratios of 3 and 4 in the Dehydration Reaction of 2[a]

Time (min)	Relative Amount	
	Alkene **3**[b]	Alkene **4**[c]
15	55	45
35	37	63
50	29	71
65	24	76
80	14	86
100	10	90
120	9	91

[a]Determined by computer integration of the GC traces for each sample.
[b]Kinetic product: retention time = 4.66 min.
[c]Thermodynamic product. Retention time = 4.77 min.

culated using the ab initio 6-31G* basis set, show an energy difference of only 1.442 kcal/mol. The ratio of **3** and **4** at equilibrium was calculated based on the equation

$$\Delta G = -RT \ln K$$

where *T* is the temperature of refluxing toluene and ΔE is used as an approximation for ΔG. A ratio of 10:90 was found and is in excellent agreement with the experimental results in Table 1.

Conclusions

During the second semester of organic chemistry, students are encouraged to develop an "independent project" (*12*). The work reported here was the project of Lesley Woods.

This experiment encompasses several topics of organic chemistry. The Grignard reaction, a staple of many organic laboratory courses, proceeds readily, gives good yields, and can be scaled down to microscale amounts. The dehydration reaction demonstrates the concept of kinetic and thermodynamic control in a reaction. Gas chromatography, the method used to monitor this reaction, gives students an introduction to separation techniques, integration of spectra, and analysis of product mixtures. Finally, the reaction lends itself well to computational study and, with further development, could be incorporated into the experiment.

Notes

1. This experiment was developed and carried out as part of the laboratory experience in the Colby College sophomore organic course.

2. The first sampling may be done sooner to observe more of the kinetic product.

3. Geometries were optimized first by MM2 calculations and further refined at the AM1 semiempirical level of theory.

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