Measuring Relative Reactivities of Electrophilic Aromatic Bromination Using a Benchtop GC-MS

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Abstract: This laboratory provides students with the opportunity to reinforce their knowledge of the numerous parameters involved in electrophilic aromatic substitution reactions. These concepts are investigated using a benchtop GC-MS. Students obtain hands-on experience with the coupling of gas-chromatographic analysis and mass-spectral analysis. Each student determines one data point by reacting a pair of compounds with bromine and iron (III) chloride. Individual results are then pooled into composite class data, affording students more available information for analysis than is typical in an organic chemistry laboratory.

Introduction

Electrophilic aromatic substitution is one of the cornerstone reactions of organic chemistry. There is a similarly rich history associated with the laboratory [1]. This reaction lends itself beautifully to demonstrating numerous important concepts, including kinetics, aromaticity, the reactivity of substituted aromatics, and the directing effects of aromatic substituents. With the availability in recent years of GC-MS in the undergraduate laboratory, one is able to use electrophilic aromatic substitution to even greater advantage by adding the ability to explore kinetics and isotope identification. Most of the chemicals are available in typical chemical stockrooms. This paper outlines an experiment where students examine the relative reactivities towards electrophilic bromination of a range of substituted benzene derivatives by using GC-MS to analyze the complex product distributions. For this experiment, the Hewlett-Packard GCD [2] was used in conjunction with ChemStation Software.

Experimental

Experimental Safety Precautions. All reactions should be carried out at room temperature without heating. The weighing and addition of bromine to the reaction should be carried out in a fume hood to prevent the inhalation of harmful fumes; gloves should be worn to prevent contact burns to the skin.

Preparation of brominated aromatic derivatives. In a 10-mL, uncapped vial, 7.8 mmol of each of the two compounds assigned by the instructor are mixed together [3]. To the mixture add 1.56 mL of nitromethane, unless durene [1,2,4,5-tetramethylbenzene] is used, in which case four times the amount of solvent must be added. Iron (III) chloride (0.66 g) is then added to the vial, which is stirred for five minutes. The solution is filtered through a glass funnel lined with filter paper into a clean, dry 20-mL uncapped vial. To this filtered solution add 0.48 mmol of Br_2 over a two-to-three minute period. It is best to weigh the bromine neat into a 10-mL capped Erlenmeyer flask, slowly transferring the liquid with a pipet and then inverting the Erlenmeyer flask into the vial and allowing it to rest on top of the vial with the vapor being somewhat contained in the system. The solution is then stirred for an additional five minutes. If fluorobenzene is used, it is necessary to allow the solution to stir for an additional ten minutes.

After the necessary stirring time, the solution is washed using 10 mL of 5% (v/v) HCl/water followed by 10 mL of water. (Note: If the competition was between toluene and ethylbenzene, then the product after the extraction will be a filmy solid that sticks to the sides of the reaction flask. The product should be dissolved in about 5 mL of ethyl ether once it has been separated from the water.) The separated organic layer is dried with calcium chloride and then decanted or pipetted away from the drying agent to be used for the GC-MS analysis. This sample is then diluted as per the instructions for the GC-MS (see supporting material) and injected.

Results and Discussion

In this experiment, each student is assigned a different 50:50 mixture, by mole percent, of two aromatic compounds. The mixture is treated with a limited amount of bromine; substitution occurs preferentially at the more reactive site(s) of the more reactive aromatic ring. Students analyze their mixtures by GC-MS and the data collected by individual students are pooled into a class data sheet to illustrate overall trends among different benzene derivatives [4]. As part of the prelaboratory exercise, each student predicts which of his or her compounds will afford the highest amount of product in addition to the preferred regioisomer, where applicable. This prediction allows them to analyze the experimental results and look for discrepancies. Because of the extreme microscale of the reaction (less than half a millimole of bromine), we decided to use the traditional brominating method of $Br_2/FeCl_3$ [5]. As long as we instruct the students to weigh out and add the bromine to their vials in the hood, we have incurred no problems with this method.

Each student is given a unique combination of two different substituted benzene derivatives (vide infra). We use toluene as the reference compound (which is assigned a reactivity of "1"), and the substituents include halogens, alkyl groups, and ethers. We also include several multiply alkylated derivatives. The students are responsible for accurately measuring out the equimolar mixture used for their particular competition studies. Some redundancy is built into the system if there are enough students in the laboratory section. Students then follow the bromination procedure as outlined for their starting sample (Two of the samples require slight modification as noted in the experimental section.) followed by analysis of their product mixture on a Hewlett-Packard GCD.

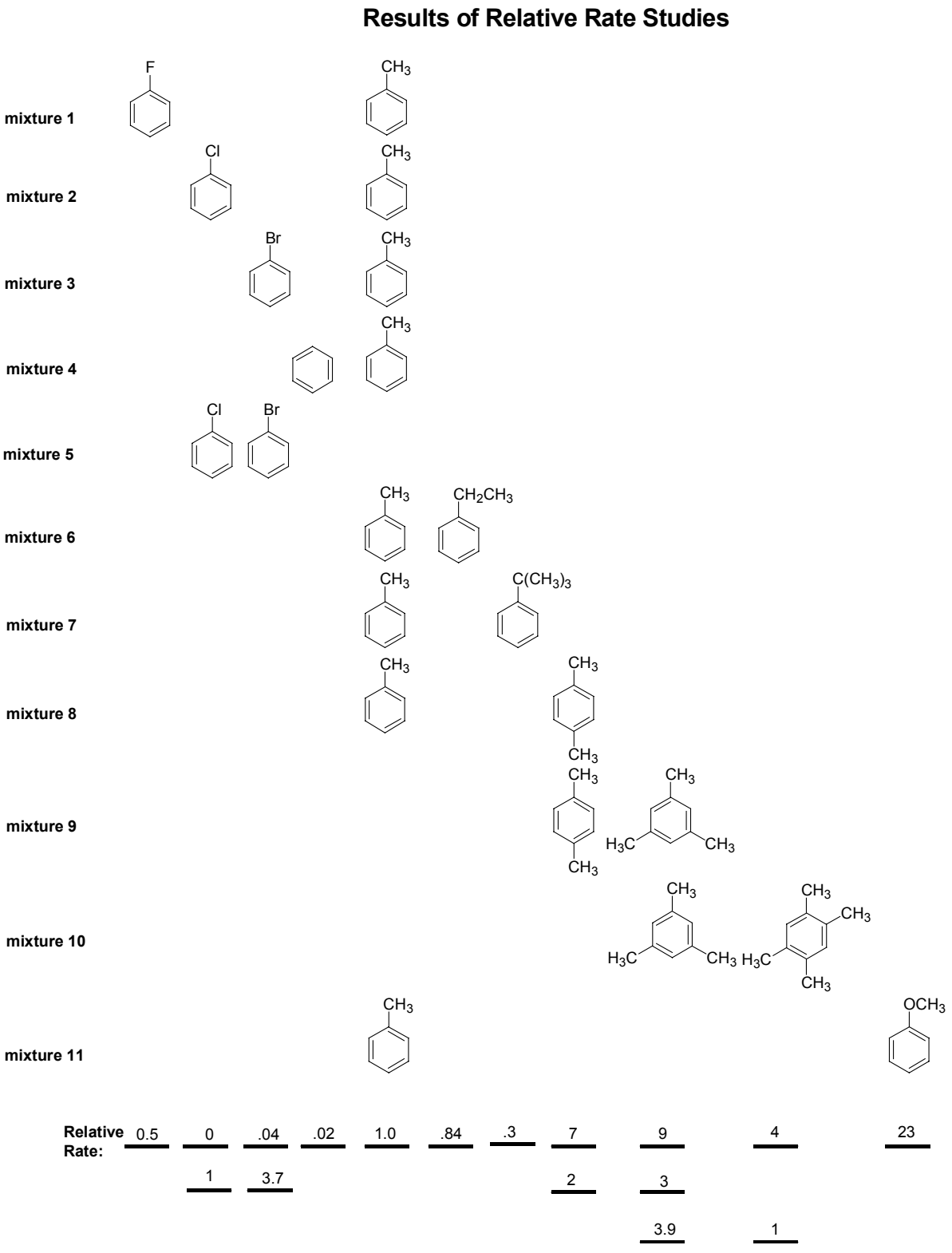

Figure 1. Class matrix for combined individual data. This is a representative example of actual class data. A blank matrix is provided in the supporting material.

This is the first experiment of our second-semester laboratory, and the students have just been introduced to mass spectrometry. We are focusing on the tandem usage of gas chromatography, with which they are very familiar, and mass spectrometry. We have set up two different methods for analysis, depending upon their assigned starting sample. At this point in the laboratory, the students are often struggling to understand the mass-spectral molecular ion regions. After the gas chromatogram appears on the screen, the student needs to look at the mass spectrum for every GC peak and determine if it is starting materials, monobrominated products, multiply brominated products, or unidentifiable material. This exercise

demands that they understand about molecular ion regions as well as isotope patterns. Their data is saved, as invariably they will need to retrieve and reprint peaks they failed to notice as important the first time. This also starts the students thinking about the shortfalls of the GC-MS, namely, the inability to tell the difference between different regioisomers. Most of them make the assumption that the smallest of the product isomers is the one classically defined as the least desirable; however, they must be aware that this is an assumption. For a few of the students, we have access to authentic product samples for a GC and these corroborate that their "hunches" about assigning regioisomers are correct.

There are several levels of analysis that we ask the students to examine. The first is simply to look at the reactivity between their two compounds. This is done by adding together all of the areas from the GC of the monobrominated products for one compound, compared to that same analysis for the second compound. Then, they calculate the relative reactivity of monobromination for their two starting materials and enter their data on a matrix as shown in Figure 1. The higher levels of analysis include (a) examining the pooled class data as a whole and (b) examining their mixture for multiply brominated products and discussing why that might or might not be expected [6].

There are other parameters of the reaction that we are not concerned with and discuss with the class ahead of time. We are not concerned with the yields in these reactions. In the prelaboratory instruction, we explain to the students about how to use internal standards to calculate the yields of the reactions if required. Our students were generally comfortable with this method because they have seen this used in the previous semester. In addition, we describe the use of standards to make sure that the GC intensities of the compounds are normalized so as not to artificially skew the numbers they obtain for product ratios. In fact, we did this ourselves during the development of this laboratory to ensure that correcting factors are not needed to obtain reasonably accurate results.

Conclusion

This laboratory reinforces to students (a) the *ortho*-, *meta*-, and *para*-directing effects of substituents, (b) the symmetry of structures and how the presence of symmetry in a molecule reduces the number of structural possibilities, (c) the activating or deactivating effects of substituents on further electrophilic aromatic substitution, (d) an easy method to calculate relative reactivities based on the product distribution, and (e) the use of gas chromatography to obtain product ratios.

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Suporting Materials. Two supporting files are available. A laboratory handout out for students (http://dx.doi.org/10.1007/s00897000411b 550223bks1.pdf) and a handout entitled *GCD Instructions for Users* (http://dx.doi.org/10.1007/s00897000411c 550223bks2.pdf).

References and Notes

1. Cason, J.; Rapoport, H. *Laboratory Text in Organic Chemistry*, **1950**, 115–122.
2. Technically the instrument is a Hewlett-Packard GCD and not a GC-MS, but as far as the students and routine users are concerned, we us these terms nearly interchangeably.
3. If there is enough instrument and laboratory time allotted, it would be useful to have students save a tiny sample of this mixture to ensure by GC later that they did indeed start with a 50:50 mixture (by mole percent), or to provide them with the correction factors if necessary.
4. It is sometimes interesting to assign two students to the same mixture as this either confirms that results are reproducible or forces them to think about why two students following the "exact same" instructions get different results.
5. Olah, G. A.; Kuhn, S. J.; Flood, S. H.; Hardie, B. A. *J. Am. Chem. Soc*. **1964**, *86*, 1039–1044. It should be noted that many other bromination methods, including "green" procedures could be tried and compared here.
6. The data presented here is not perfect data, but rather actual class data.