Molecular Modeling and Nuclear Overhauser Enhancement Spectroscopy (NOESY): Tools for Studying the Regioselective Bromination of 3-Bromoanisole

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Abstract: The use of molecular modeling for predicting chemical reactivity has been highly successful in the industrial and academic research communities. For this reason, increased emphasis has been placed on molecular modeling in the undergraduate curriculum. In the described experiment, the bromination of 3-bromoanisole, students are encouraged to use molecular modeling software as a tool for predicting chemical reactivity. Besides introducing students to molecular modeling, this experiment incorporates the use of nontraditional, less hazardous reagents and solvents for electrophilic aromatic bromination reactions. Lastly, nuclear Overhauser enhancement spectroscopy (NOESY) is introduced as a tool for structural elucidation. Although there are a number of aspects to this experiment, two 3-hour laboratory periods are sufficient because the results from semiempirical (AM1) geometry optimizations, which are complete in seconds, were almost identical to the higher order, more time-intensive ab initio (3-21G*) calculations. In addition, the experimental time was greatly shortened by the discovery that catalytic HCl(aq) reduces the reaction time from 5 hours to 18 minutes.

Introduction

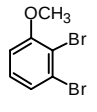
Advances in computers and programming have resulted in the development of easy to use molecular modeling and NMR processing software. As a result, it is common for undergraduate students to use molecular modeling [1] and FT NMR [2] in a variety of courses. This paper describes an undergraduate experiment which utilizes both tools for studying the regioselectivity of the bromination of 3-bromoanisole. The experiment consists of three parts: (1) the use of molecular modeling (Wavefunction's SPARTAN was chosen for its ease of use) as a tool for predicting the regioselectivity of the bromination of 3-bromoanisole; (2) a novel procedure for performing electrophilic aromatic bromination reactions using *N*-bromosuccinimide (NBS), acetone, and catalytic HCl(aq); and (3) the use of 1-D and 2-D (NOESY) ^{1}H NMR experiments for structural determination. We have used this experiment in an undergraduate synthesis course populated by juniors and seniors. We feel, however, that the experiment is appropriate for use in an introductory organic course provided that most of the techniques have been introduced in previous experiments or in classroom discussions.

Background

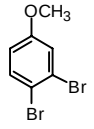
Bromination Studies. Electrophilic aromatic bromination reactions have traditionally been accomplished using molecular bromine. *N*-bromosuccinimide [3] was chosen as an alternative because unlike molecular bromine, NBS is not a strong oxidant, it is not volatile, and it does not readily generate hydrogen bromide gas. However, previously reported procedures using NBS for aromatic substitution reactions are inappropriate for use in the undergraduate laboratory because of solvent toxicities and lengthy reaction times. We have addressed both of these problems.

The most commonly used solvents, carbon tetrachloride [4], a known carcinogen and ozone depleter, and *N*,*N*-dimethylformamide [5], a high-boiling toxic substance, have been replaced by acetone. In addition, we have found that HCl(aq) catalyzes electrophilic aromatic brominations in this solvent [6]. This results in an 18-min reaction when 3-bromoanisole is used as the substrate, compared to 5 h in refluxing acetone without the catalyst. We also found that the reaction mixture, which turns yellow upon addition of 1 M HCl(aq), becomes colorless once the reaction is complete. And lastly, the byproduct, succinimide, can be easily removed by concentrating the crude reaction mixture, adding petroleum ether or hexanes to the resulting oil, and then filtering the precipitated succinimide. These conditions make this method extremely convenient for students to perform in the laboratory.

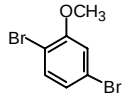
Molecular Modeling Studies. The electrophilic bromination of 3-bromoanisole using NBS in acetone with catalytic HCl(aq) yields three isomeric dibromoanisoles, as determined by GC/MS. Assuming that the product distribution of this electrophilic aromatic substitution (EAS) reaction is under kinetic control, the three expected products would be 2,3-dibromoanisole, 3,4-dibromoanisole, and 2,5-dibromoanisole. However, one compound predominates. In an effort to explain why one isomer predominates, molecular modeling was used.



2,3-dibromoanisole



3,4-dibromoanisole



2,5-dibromoanisole

Figure 1 shows the most common mechanism for an EAS reaction. The rate-limiting step for most EAS reactions has been determined to be the formation of the sigma complex [7]; it is assumed to be so in this study.

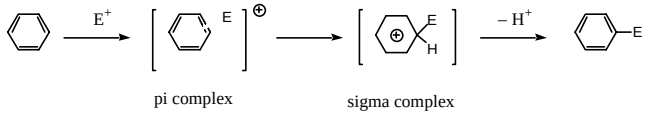
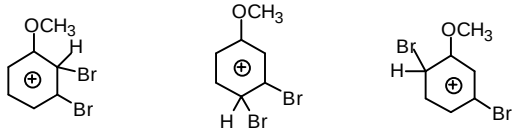


Figure 1. Accepted mechanism for EAS reactions.



A **B** **C**

Figure 2. Possible sigma complexes.

The possible sigma complexes, **A**, **B**, and **C**, that would be generated in the bromination of 3-bromoanisole are shown in Figure 2. Based upon Hammond's postulate, it can be assumed that the energy differences between the possible transition states for the formation of the sigma complexes would be similar to the differences in energy of the sigma complexes for this endothermic step. Therefore, the differences in energy between the sigma complexes would be similar to the activation energy differences for their formation. Knowing that the reaction with the lowest activation energy would proceed at the fastest rate, a prediction can then be made about the favored pathway [8].

Spectral Analyses. Identification of the product (i.e., the determination of which isomer) was inconclusive based upon analyses of the MS, IR, and ^{1}H NMR spectra. Therefore, a NOESY spectrum (2-D NOE experiment) was distributed to the students. Although a 1-D NOE difference experiment provided the information necessary for structural determination, we chose to distribute the NOESY spectrum because few simple examples of NOESY's utility are available for use in the undergraduate laboratory.

The NOESY experiment [9], which is commonly used to determine substitution patterns and stereochemistry, is based upon the observation that through-space spin-state relaxation and enhancement by a dipole–dipole mechanism may occur between nuclei that are close together (less than 5 Å). The resulting NOESY spectrum is interpreted in the same manner as spectra from other 2-D experiments, such as COSY.

Experimental

A copy of a handout for students (510020bas1.pdf), full-page spectra (510020bas2.pdf), and the outputs from the AM1 calculations (510020bas3.pdf) have been included with this paper.

General. The reported calculations were carried out using MacSPARTAN on an Apple Macintosh PowerBook G3 (266 MHz). The students used Pentium II PCs (266 MHz) running PC SPARTAN Plus. *N*-Bromosuccinimide and 3-bromoanisole were purchased from Aldrich Chemical Company and used without further purification. Acetone was purchased from Valley Industries, Bartonville, IL. One-dimensional NMR spectra were taken on a Varian EM360 (60 MHz for ^{1}H, 15.09 MHz for ^{13}C) equipped with Anasazi Instruments' FT upgrade. The NOESY spectrum was taken on a Varian Unity Inova-500 (500 MHz) and collected in 2 × 200 increments, which required 5.5 h when using a 4.000-s relaxation delay and a 2.000-s mixing time. The NOE difference spectrum was obtained on a Bruker ARX 400 spectrometer (400 MHz). Mass spectra (70 eV)were obtained on a Hewlett Packard 5890/5970 GC/MS, using a HP-1 (cross-linked methyl silicone gum) 25 m × 0.2 mm × 0.5 μm (film thickness) column with helium as the carrier gas. The oven temperature program was 100 °C for 2 min, increased at 50 °C per min for 2 min, then held at 200 °C for 6 min, for a total run time of 10 min. (A reviewer suggested collecting one set of GC/MS data and posting it electronically. Wsearch could then be used to process the data remotely.) IR spectra were obtained on a Nicolet 210 FT-IR spectrometer [10]. Product distributions were calculated from GC peak areas obtained on a Hewlett Packard 5890 GC equipped with an FID. No corrections were made for FID response factors. Identical chromatography conditions were used for both GC and GC/MS.

Molecular Modeling Procedure. The heats of formation were calculated using MacSPARTAN or PC SPARTAN Plus AM1 geometry optimization (charge = 1, multiplicity = 1). The Hartree–Fock energies were calculated using MacSPARTAN or PC SPARTAN Plus 3-21G* geometry optimization (charge = 1, multiplicity = 1).

Bromination Procedure. To a small test tube were added 1.0 mmol of 3-bromoanisole and 2 mL of acetone. The test tube was then placed in a water bath at 25 °C, and 1.0 mmol of *N*-bromosuccinimide and a magnetic stir bar were added. After the NBS dissolved, 1 drop of 1 M HCl was added. The reaction mixture was stirred at room temperature until the yellow color disappeared, at which time the reaction was complete. (If more than one equivalent of NBS is added, the color may not disappear.) The reaction mixture was concentrated by rotary evaporation (a water bath at 70–80 °C can also be used). To the resulting oil was added 3 mL of hexanes; after stirring at room temperature for 5 min the mixture was cooled in an ice bath. The precipitate, which is succinimide, was gravity filtered and the filtrate collected in a preweighed test tube. Removal of the hexanes, via rotary evaporation, yielded the crude product, which was analyzed without further purification.

3,4-dibromoanisole. ^{1}H NMR ($CDCl_3$, δ): 7.43 (d, 1 H, J = 8.8 Hz), 7.12 (d, 1 H, J = 2.9 Hz), 6.67 (dd, 1 H, (J = 8.9, 2.9 Hz), and 3.73 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, δ): 158.763, 133.306, 124.533, 118.679, 114.724, 114.529, and 55.290 ppm. IR (neat): 3088, 3006, 2960, 2936, 2835, 1586, 1561, 1466, 1437, 1286, 1261, 1227, 1000, 1036, 907, 848, 801, and 733 cm^{-1}. MS: *m/z* (relative intensity): 268, 266, 264, 253, 251, 249, 225, 223, 221, 172, 170, 157, and 63.

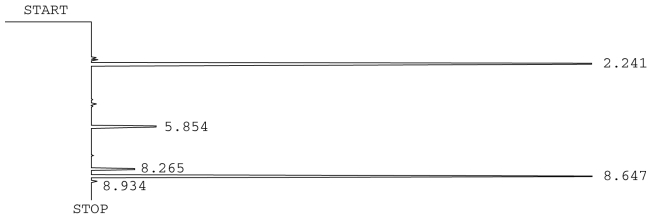
Results and Discussion

The heats of formation and total molecular energies (i.e., Hartree–Fock energies) of the sigma complexes were calculated using MacSpartan. Both semiempirical (AM1) and ab initio (3-21G*) calculations (geometry optimizations) were performed. As Table 1 reveals, the calculated energy differences between the sigma complexes were similar for AM1 and 3-21G* calculations. Therefore, only the much less time-intensive AM1 calculations were performed by students. (Note: the heat of formation of the sigma complex necessary for the formation of 3,5-dibromoanisole is 193.951 kcal mol^{-1}.)

As Table 1 shows, semiempirical (AM1) calculations reveal that sigma complex **B** is 2.600 and 2.369 kcal mol^{-1} more stable, respectively, than sigma complexes **A** and **C**. Assuming that the differences in the heats of formation are similar to the differences in the free energies (G_{diff}) of the complexes, a product ratio can be determined using the relationship $G_{diff} = -RT \ln K$. Therefore, the expected product ratio (3,4-dibromo-anisole: 2,3-dibromoanisole: 2,5-dibromoanisole) would be 80.72:1:1.48, or 97% 3,4-dibromoanisole to 3% other dibromoanisole isomers. This assumption seems reasonable because the entropies of the sigma complexes should be similar and therefore $G_{diff} \approx H_{diff}$. The computation results correlate very well with the experimental values of 94%

Table 1. Computational Times, Energies, and Ratios of Sigma Complexes

	AM1	3-21G*
Energy of A	180.004 kcal mol^{-1}	–5462.362024 hartree
Computational time	13 s	5 h, 36 min
Energy of B	177.404 kcal mol^{-1}	–5462.368123 hartree
Computational time	11 s	2 h, 9 min
Energy of C	179.773 kcal mol^{-1}	–5462.364574 hartree
Computational time	9 s	2 h, 2 min
E_{diff} between B and A (cal mol^{-1})	–2600	–3827
E_{diff} between B and C (cal mol^{-1})	–2369	–2227
Ratio of B:A	80.72:1	641.3:1
Ratio of B:C	54.64:1	42.99:1
Percentage of 2,3-dibromoanisole	1.20%	0.15%
Percentage of 3,4-dibromoanisole	97.02%	97.58%
Percentage of 2,5-dibromoanisole	1.78%	2.27%



RT	AREA	TYPE	WIDTH	AREA%
1.931	131	PV	.019	.00313
1.965	132	VV	.019	.00315
2.040	215	VP	.020	.00513
2.241	4118150	PB	.025	98.24794
2.415	2356	BB	.019	.05621
4.338	163	VV	.043	.00389
4.556	445	VV	.041	.01062
4.633	117	VV	.041	.00279
4.698	144	VV	.047	.00344
5.854	3629	VV	.031	.08658
5.934	114	VP	.039	.00272
7.537	365	PP	.046	.00871
8.265	3580	PP	.047	.08541
8.647	61521	PB	.051	1.46772
8.934	528	BP	.052	.01260

Figure 3. GC (FID) of crude product (dilute solution in THF). THF R_t = 2.24, starting material (3-bromoanisole) R_t = 5.85, and R_t = 8.265, 8.647, and 8.934 for the three dibromoanisole isomers. The identities of the peaks were determined by GC/MS.).

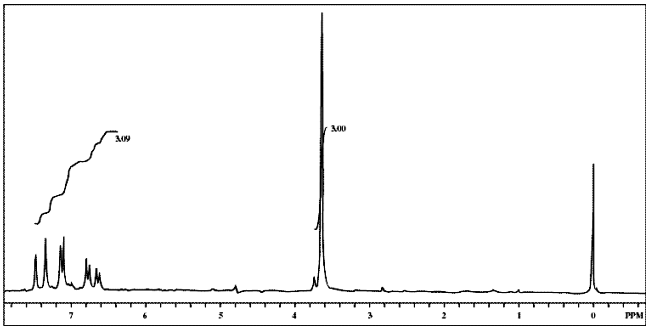


Figure 4. 60-MHz NMR spectrum of crude product.

3,4-dibromoanisole to 6% other dibromoanisole isomers as determined by GC (Figure 3).

Spectral Analysis. The last aspect of this experiment was to unequivocally determine that the major product of the reaction was the predicted 3,4-dibromoanisole. By analyzing the ^{1}H NMR aromatic proton splitting pattern (Figure 4), 2,3-dibromoanisole can be eliminated from consideration as the major product because three doublets of doublets would be expected for this isomer whereas two doublets and a doublet of doublets are observed. However, spectra of both 3,4-dibromoanisole and 2,5-dibromoanisole would have this splitting pattern. Differentiation of 3,4-dibromoanisole and 2,5-dibromoanisole based upon chemical shift differences of the aromatic protons is also inconclusive. The calculated chemical shifts of the aromatic protons for 2,5-dibromoanisole are 7.76, 7.61, and 7.26 ppm; for 3,4-dibromoanisole they are 7.71, 7.61, and 7.26 ppm [11]. In addition, comparison of experimental ^{13}C shifts to calculated ^{13}C shifts was inconclusive. Because the two isomers could not be differentiated based upon analysis of 1-D NMR spectra, a NOESY spectrum (2-D NOE experiment) was distributed to the students. For the molecules in question, the correlations in the NOESY spectrum between the protons of the methoxy group and the aromatic protons ortho to the methoxy group provide the information necessary for structural determination, because 2,5-dibromoanisole would only have one correlation whereas, 3,4-dibromoanisole would have two. As seen in Figure 5, two correlations were observed between the methoxy protons (3.8 ppm) and aromatic protons (7.2 and 6.7 ppm), thereby proving that the major isomer is 3,4-dibromoanisole.

Conclusion

The bromination of 3-bromoanisole using NBS in acetone with catalytic HCl(aq) is an ideal experiment for introducing molecular modeling and 2-D NMR to undergraduates. The reaction proceeds quickly and cleanly, leaving ample laboratory time for molecular modeling studies and for spectra collection. In addition, the computational results are in excellent agreement with the experimental results, providing an opportunity for students to see how molecular modeling can be used as a chemical reactivity predictor.

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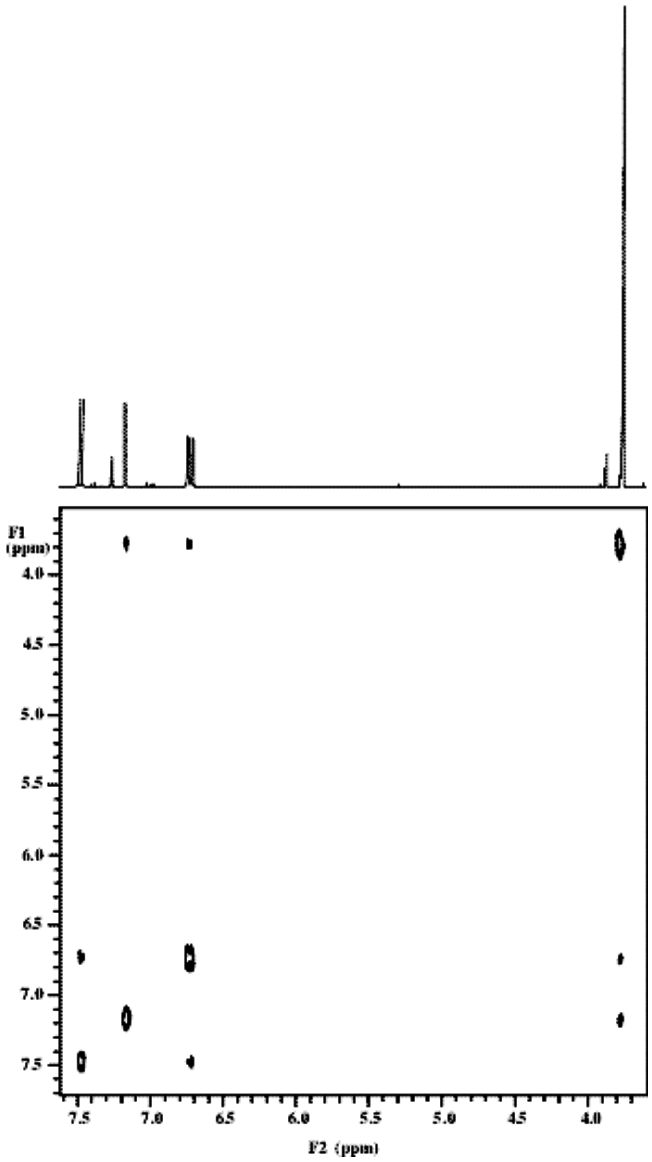

Figure 5. 500-MHz NOESY spectrum of crude product. (Diagonal peaks due to the minor isomers have been removed.)

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