Syn and Anti Isomer Preference in Oximes: An Undergraduate Organic Chemistry Experiment

Michael D. Mosher* **and Scott Meisenbach**

Department of Chemistry, University of Nebraska at Kearney, Kearney, NE, 68849-1150, mosherm@unk.edu

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Abstract: An experiment is described that links a nucleophilic carbonyl addition reaction to a study of structure–activity relationships. Students prepare a series of oximes (from readily available ketones and aldehydes) and, with the use of NMR, define the ratio of syn and anti isomers formed in the reaction. From these data, a quantitative assessment of the steric hindrance of hydrogen, methyl, ethyl, isopropyl, and *t*-butyl can be obtained.

Background and Introduction

A quantitative study of the effects of substitution on the behavior of a molecule (be it chemical or physical properties) is known as a quantitative structure–activity relationship (QSAR). QSARs have been utilized in basic research to assist in the determination of reaction mechanisms. They have also been implemented in the modification of existing drugs to provide more effective alternatives. In fact, the discipline of medicinal chemistry relies on QSAR to a great degree. Properties of substituent groups, such as their steric size, surface area, and polarizability, are assigned quantitative values in QSAR treatments, and those values are correlated to some observable property in a series of molecules (i.e., reactivity, efficacy versus disease, toxicity, and carcinogenicity).

Steric hindrance is one of the major molecular effects discussed in organic chemistry courses. It is used to help define how the size of a substituent relates to the reactivity of a particular molecule. The effect of steric hindrance in the outcome of a reaction was first noted in 1879 [1]. Meyer [2], in 1895, proposed a method to quantitatively assign steric hindrance in the esterification of substituted benzoic acids (using the atomic weights of ortho substituents). The volume of the substituents has been argued as a better descriptor of steric hindrance [3]. Since that time, various attempts to deal with steric hindrance in a quantitative sense have been made [4].

By dealing with electronic and steric properties separately, Taft was able to more clearly define structure activity relationships [5]. Examination of the hydrolysis of esters under acidic conditions led to his development of the σ^* parameter (the inductive-field effect). The σ^* parameter contains the steric parameter shown in eq. 1. This parameter (E_s) relates the rate of hydrolysis of a substituted ester versus that of an unsubstituted ester. This relationship is an indicator of the steric bulk about the carbonyl reaction center.

$$E_s = \log\left(\frac{k_x}{k_H}\right)_A \qquad (1)$$

Charton envisioned another approach to defining steric hindrance. His steric parameter, υ_x, was based on the minimum van der Waals radius of the substituent compared to the radius of hydrogen (eq 2) [6]. While this parameter does a good job in defining the steric bulk of methyl, *t*-butyl, and other symmetrical substituents, this approach to defining steric bulk becomes difficult for unsymmetrical substituents. The parameter is defined as

$$\upsilon_x = r_v X - 1.20 \qquad (2)$$

where r_vX is the minimum van der Waals radius of substituent *X*. Many other examples of steric parameters exist [7, 8]

The idea of steric hindrance is usually implemented in the organic chemistry lecture in a qualitative sense. It is used to illustrate the potential-energy relationships among the various conformations of butane, the greater stability of equatorial versus axial substitution on cyclohexane ring systems, and the difference in rates between S_N2 reactions (see eq 3) [9]; however, little quantitation of the differences in the substituents is provided.

$$CH_3 < CH_3CH_2 < (CH_3)_2CH < (CH_3)_3C \qquad (3)$$

To address this deficiency, we envisioned the generation of a laboratory experiment that would use QSAR to quantitatively develop the relationship observed in eq 3. A search of the literature yielded a few published experiments for the organic laboratory that show qualitative effects of steric hindrance on reactivity. For example, the determination of the relative rate of substitution of alkyl halides [10] was identified as a good example of a qualitative laboratory; however, this and other laboratory experiments do not provide quantitative correlation between the reaction rate and the substituent with terms such as E_s. An obvious need exists to implement a laboratory experiment that covers structure-reactivity relationships in greater detail.

The reaction to form an oxime from commercially available aldehydes and ketones is a good reaction system for introducing quantitative steric effects. Oximes may be discussed in the organic chemistry lecture as a product of the reaction of hydroxylamine with a ketone or aldehyde. The mechanism of the reaction involves two major steps (see Figure 1): the addition of hydroxylamine to the carbonyl group, and the elimination of water from the intermediate.

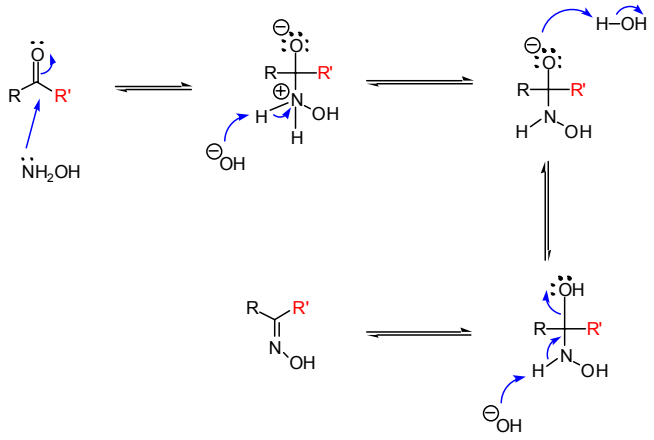

Figure 1. Mechanism of oxime formation. (The mechanism described here is the base-catalyzed mechanism. Rate studies indicate that oxime formation is most rapid at pH = 4.)

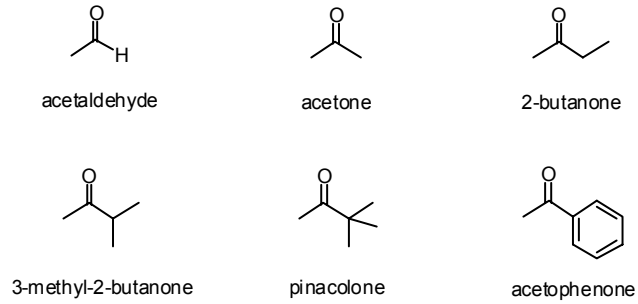

Figure 2. Structures of the compounds used in this experiment.

Table 1. List of Compounds and Steric Parameters Used in the Experiment

Compound	E_s[a]	υ_x[b]	Substituent
Acetaldehyde	0.00	0	H
Acetone	–1.24	0.52	methyl
2-Butanone	–1.31	0.56	ethyl
3-Methyl-2-butanone	–1.71	0.76	*i*-propyl
Pinacolone	–2.78	1.24	*t*-butyl
Acetophenone	–3.43	0.57	phenyl

[a] The steric parameters are based on the nonmethyl substituent. [b] The steric parameters are based on the volume of the nonmethyl substituent according to Charton.

Table 2. Average Syn and Anti Oxime Ratios Determined by ^{1}H NMR (Syn is defined here as the nonmethyl substituent residing cis to the OH group of the oxime)

Compound	CH_3 Signal Location (ppm)	% syn[a] (calc)	% syn[b] (lit)
Acetaldehyde	1.62; 1.47	63	61
Acetone[c]	1.73, 1.72	50	50
2-Butanone	1.75, 1.73	29	26
3-Methyl-2-butanone	1.76, 1.73	19	9
Pinacolone	1.86, 1.68	1	0
Acetophenone	2.61, 2.34	15	6

[a] These values were determined from the experimental data collected in this work. [b] These values were obtained from reference 12. [c] Acetone is symmetrically substituted; thus, it should not be considered as a mixture of syn and anti isomers. It is included here to aid in the preparation of the structure–reactivity relationship.

Because the reaction is typically carried out under conditions that favor thermodynamic control, the effect of steric bulk on the product distribution most likely arises due to the difference in the thermodynamic stabilities of the syn and anti products. Given that the syn product would exhibit more steric hindrance, it is thus less stable than the anti product, and it is predicted to exist as the minor component of the product mixture.

The experiment outlined below describes a laboratory experiment based on an existing study [12] of the stereochemical outcome of the reaction of hydroxylamine with substituted aldehydes and ketones. The experiment illustrates the use of standard organic chemistry equipment, a straightforward workup procedure, and the use of a common derivative to the determination of stereochemical concerns in a reaction. The experiment also includes the use of ^{1}H NMR and ^{13}C NMR in the undergraduate laboratory.

Experimental Procedure

Students work individually to prepare a single oxime from a list (see Figure 2 and Table 1.) of available aldehydes and ketones using the conditions of thermodynamic control to determine the outcome of the reaction. In a class of 18 students, each of the oximes of the compounds listed in the table is analyzed three times in order to provide the entire set of data for quantitative correlation. The oximes are easily prepared according to published procedures (see supplementary material for the experimental method). Simple extractive isolation and evaporation provides the desired oximes as a mixture of syn and anti stereoisomers (> 95% yield). Further purification of the product mixtures is not performed [11]. The ratio of oxime isomers in the product mixture is measured by ^{1}H NMR and/or ^{13}C NMR and compared to the ratios determined by the other students in the laboratory. Because each oxime is prepared and analyzed multiple times, a reduction in the error associated with the incorrect measurement of NMR integration ratios is obtained.

Once the average ratios of syn and anti oximes are found, the information is correlated to the steric parameters indicated in Table 1. Sample information determined from ^{1}H- NMR analysis of the compounds is shown in Table 2. The percent syn isomer was obtained by comparison of the integration of the methyl signal that corresponded to the two stereoisomers. Alternative comparison of the integration of the methyl signal in the ^{13}C NMR provided similar results.

In almost every case, the methyl signal for the syn isomer did not overlap with that of the anti isomer. In those cases where signal overlap was apparent, an alternate signal was compared (see the supplementary material for an example of this.) The student-calculated values for the percent syn isomer compare well to values found in the literature (Table 2) [13].

Correlation of the results by the students can be accomplished using Microsoft Excel, Kaleidograph, Cricket Graph, Delta Graph or other similar graphing programs. An example of the correlation, completed using MS Excel, is shown in Figures 3 and 4. From the correlation coefficient (R^2), obtained by noting the graphical trend of the results, it is made apparent that the volume (size) of the substituent is a better indicator of the stereochemical outcome of the thermodynamically controlled formation of an oxime (compare Figure 3 to Figure 4). Students then can be asked to estimate the approximate syn/anti ratio of oximes that would form under these conditions for a series of methyl ketones. Given the E_s and υ_x values and the completed QSAR for these new substituents, this process is relatively straightforward.

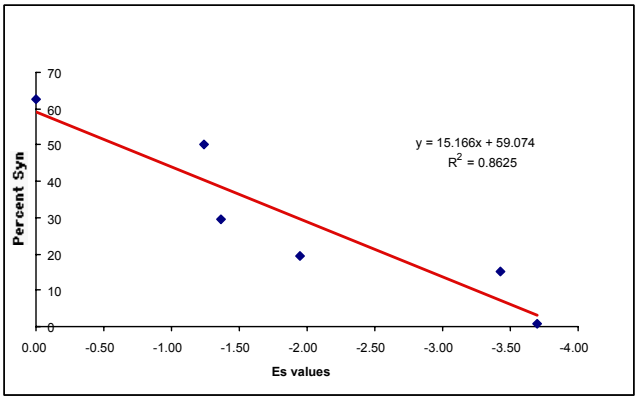

Figure 3. Correlation of E_s with percent syn. Note the relatively poor correlation coefficient.

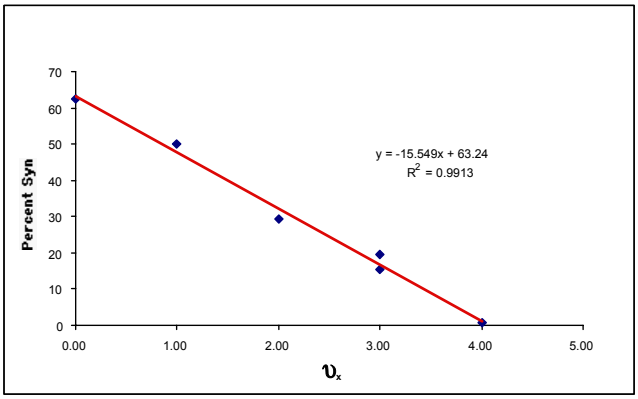

Figure 4. Correlation of Charton's parameter (υ_x) with percent syn. Note the relatively high correlation coefficient.

Conclusion

Reiteration of the general experimental procedure (reflux setup, extraction, evaporation), detailed explanation of the mechanism of an important reaction in organic chemistry, and the use of NMR to measure ratios of products in a mixture helps to strengthen a student's skills in the organic laboratory. Moreover, the chance to incorporate a quantitative structure–reactivity relationship into the undergraduate organic chemistry laboratory can be a useful way to emphasize how the structure of a molecule relates to its reactivity. The experiment described above clearly allows one to illustrate a structure-versus-reactivity relationship and provides the student with a better understanding of the mechanism of nucleophilic addition to a carbonyl.

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Supporting Materials. A detailed experimental procedure, a student handout, and a sample proton NMR spectrum (with integration) are included in a zip file (http://dx.doi.org/10.1007/s00897000623b).

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