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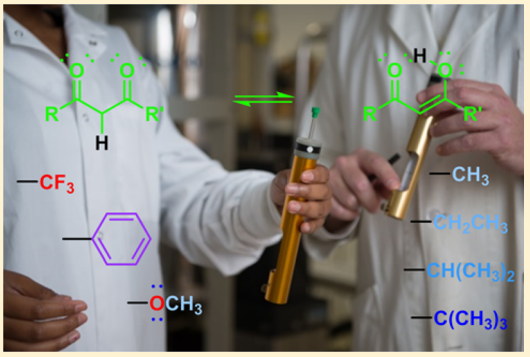
Measuring Structural and Electronic Effects on Keto–Enol Equilibrium in 1,3-Dicarbonyl Compounds

Kyle T. Smith, Sherri C. Young,[†] James W. DeBlasio, and Christian S. Hamann*

Department of Chemistry, Albright College, Reading, Pennsylvania 19104, United States

Supporting Information

ABSTRACT: Nuclear magnetic resonance (NMR) spectroscopy is an integral part of the undergraduate chemistry curriculum. In addition to structure determination, NMR spectroscopy is used to analyze chemical reactions and equilibria in situ. Determination of the position of equilibria is well-suited to NMR analysis in the undergraduate laboratory as an extension of peak identification and signal integration, and the determination of keto–enol equilibrium remains a popular undergraduate laboratory experiment. Several factors affect the position of keto–enol equilibrium, defined here as $K_{e/k}$ = [enol]/[keto], including structure (steric bulk, conjugation, electron-withdrawing/donating groups, resonance), temperature, and solvent. A judiciously selected set of compounds that have a common 1,3-dicarbonyl moiety with progressively changing ligands at the 1 and 3 positions is presented. This array allows students to investigate structure–function relationships that affect keto–enol equilibrium in a cumulative fashion and affords instructors a broad selection of compounds for study in both introductory and advanced laboratory courses using a variety of pedagogic approaches.



KEYWORDS: *Constitutional Isomers, Equilibrium, Hands-On Learning/Manipulatives, Laboratory Instruction, NMR Spectroscopy, Organic Chemistry, Physical Chemistry, Problem Solving/Decision Making, Second-Year Undergraduate, Upper-Division Undergraduate*

INTRODUCTION

Tautomers are a special case of structural isomerism in which a change in the position of one double bond (in this case, C=O versus C=C) and one hydrogen atom (C–H versus O–H) results in a pair of constitutional isomers.[1] An historically important example of tautomerization is that which occurs in the purine and pyrimidine bases of DNAs. Knowledge of these systems was a key development in the proposal of Watson–Crick base pairs and the structure of DNA.[2] Organic synthesis experiments in this *Journal* rely on students' knowledge of factors affecting keto–enol equilibria,[3a] and one author has developed a mnemonic to promote mastery of the mechanism of keto–enol tautomerization.[3b]

1,3-Dicarbonyl compounds exhibit keto–enol tautomerization (Figure 1).[4] An historically fruitful system for the study of tautomerism using NMR spectroscopy in the undergraduate laboratory is pentane-2,4-dione (Figure 2, compound **A**). Previous papers in this *Journal* have focused on the effects of structural elements, including aromatic conjugation and electron-withdrawing/donating groups, on $K_{e/k}$, the equilibrium constant for keto–enol tautomerization; solvent, temperature, concentration effects, kinetics, and isotope exchange have also been explored.[5] The experiment described herein provides a complementary investigation in which students considered the effects on $K_{e/k}$ from steric bulk, electron-withdrawing groups, and lone-pair electron conjugation in compounds substituted at the 1 and 3 positions (relative to the dicarbonyl moiety; Figure 2).

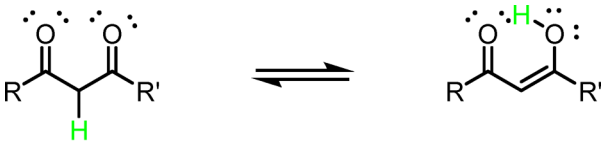


Figure 1. Keto–enol tautomerization of a generic 1,3-dicarbonyl compound. The enolizable hydrogen is highlighted in green. The R and R′ groups explored by students in this experiment may be found in Figure 2.

The goal for this experiment was to demonstrate the power of NMR spectroscopy to determine the thermodynamic parameter of equilibrium constant by moving students beyond the 1 sample = 1 analyte paradigm. To determine $K_{e/k}$, students integrated the NMR signals corresponding to the enol hydrogens and those corresponding to the keto hydrogens (eq 1). By definition,

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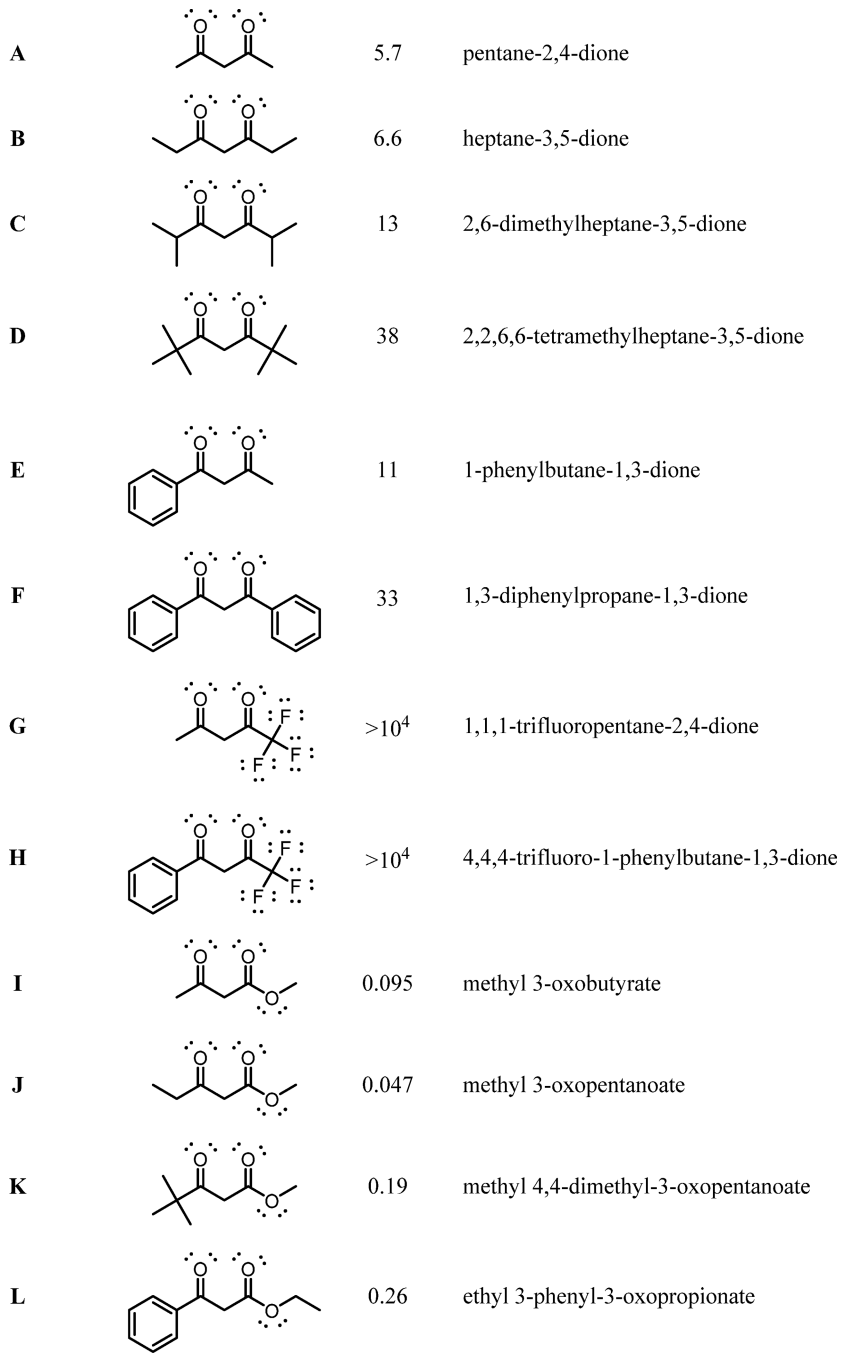

Figure 2. Representative $K_{e/k}$ values obtained by students for 1,3-dicarbonyl compounds.

$$K_{e/k} = \frac{[\text{enol}]}{[\text{keto}]} = \frac{(\text{sum of enol integrals})/(\#\text{ of enol hydrogens integrated})}{(\text{sum of keto integrals})/(\#\text{ of keto hydrogens integrated})} \quad (1)$$

When $K_{e/k} > 1$, the conditions favor the enol form, and when $K_{e/k} < 1$, the conditions favor the keto form. Ideally, all of the enol hydrogens and all of the keto hydrogens would be resolved and integrated separately. Intentional inclusion of the normalization factor (that is typically implied) allowed $K_{e/k}$ to be calculated from all or a subset of resolved signals. Thus, the sum of the enol peak integrals divided by the sum of the keto peak integrals (both normalized for the number of hydrogens in each set of peaks) yields $K_{e/k}$ even when baseline resolution of signals was not possible. This approach expanded the number of compounds available for analysis and emphasized for the students the importance of looking beyond simplifying assumptions.

EXPERIMENT

Students worked simultaneously in a classroom and in the NMR room. In the classroom, students worked through a series of NMR structure predictions for the compounds under investigation (the laboratory handout is provided in the Supporting Information). In pairs students were brought into the NMR room where they collected their own data, which were photocopied and shared with the class for analysis

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including comparison to prediction. This combination of classroom and laboratory provided all students with focused activity, a feature they appreciated (as compared to crowding the NMR room or setting students adrift when it was not their turn on the instrument). Students used model kits to build pentane-2,4-dione and the other structures in both the keto and the enol form, and focused their attention on predicting the effect of different structural elements on $K_{e/k}$ based on their knowledge of keto−enol equilibrium, pK_a, or other chemical reactivity (for example, aldol and Claisen condensations[6]). Students were required to go beyond the correlation tables found in most undergraduate texts[7] to make correct peak assignments; at times they relied on relative integral values to make assignments. At the end of the period or in a different laboratory or lecture period, students accumulated their data (essentially preparing Figure 2) for comparative analysis and discussion.

Several versions of this experiment have been performed over many semesters by approximately 100 students in an introductory organic chemistry course (4-h laboratory format; up to 15 students per section) with much success. Students typically made single determinations from samples prepared by the instructor or student assistant; representative data are presented in Figure 2. The experiment may be modified to accommodate shorter laboratory periods, perhaps by selecting a subset of structurally related compounds.

HAZARDS

A summary of the MSDSs for the chemicals used in this experiment may be found in the Supporting Information. Many of the chemicals used in this experiment are hazardous in case of skin or eye contact, inhalation, or ingestion. Sample volumes are small, reducing risks of exposure. Students who prepare samples should wear goggles and gloves (nitrile) and work in a fume hood when handling these chemicals. Proper precautions should be taken when handling glass NMR tubes and when working in the NMR laboratory. Furthermore, several of the compounds are combustible and/or flammable liquids. Therefore, open flames are prohibited when this experiment is being performed.

RESULTS AND DISCUSSION

Evaluating the Effect of Steric Bulk

Compounds **A**−**D** were selected to evaluate the effect of aliphatic steric bulk on $K_{e/k}$. From this set of congeners, students evaluated the effect of R = R′ = $-CH_3$ (methyl, **A**), $-CH_2CH_3$ (ethyl, **B**), $-CH(CH_3)_2$ (isopropyl, **C**), and $-C(CH_3)_3$ (*t*-butyl, **D**) groups on $K_{e/k}$. Note that while steric bulk increases in this series, the issue is not complicated with the possibility of aromatic conjugation (see below). In the cases of **B** and **C**, students relied on their knowledge of spin−spin splitting as they made their peak assignments.[8]

These data suggested that increasing aliphatic steric bulk increased stability of the enol structure ([enol]:Me ≈ Et < iPr < *t*-Bu). The range (∼7-fold) was small compared to other effects investigated in this and other reports.[5] By comparing molecular models for R = R′ = $-CH_3$ (methyl) with R = R′ $-C(CH_3)_3$ (*t*-butyl), students were able to rationalize that the keto form appears to have a steric clash that is somewhat relieved in the enol form.

Evaluating the Effect of Electron-Withdrawing Groups

Compounds **E**−**H** were selected to highlight the effect of electron-withdrawing groups on $K_{e/k}$. Students observed that the electron-withdrawing groups favored the enol form, consistent with the result for 3-cyanopentane-2,4-dione (not shown).[5k] The effect of two phenyl groups (**F**) is approximately the same as the *t*-butyl groups (**D**) but much less than that of the trifluoromethyl group (**G**). Students were able to note that the effect is cumulative (**F**, **H**; see below).

Evaluating the Effect of Electron Donation via Lone Pair Resonance

Organic chemistry students learn the effects of lone pair resonance on the acidity of α hydrogens (as measured by the acid dissociation constant, K_a) when studying aldol and Claisen condensations, as well as the acetoacetic ester synthesis and related reactions. Esters stabilize the carbonyl carbon by resonance (Figure 3), which has the net effect of stabilizing the keto form.[6]

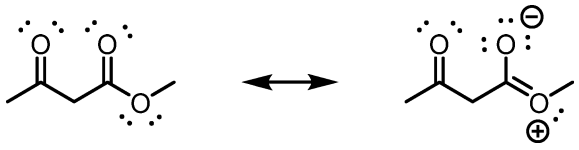

Figure 3. Electron donation via lone pair resonance in methyl 3-oxobutyrate (**I**), resulting in stabilization of the keto form.

A set of compounds was selected representing a coordinate study of the effects of lone pair conjugation on the position of keto−enol equilibrium, methyl 3-oxobutyrate (**I**), methyl 3-oxopentanoate (**J**), and methyl 4,4-dimethyl-3-oxopentanoate (**K**). In this series, the methoxy group shifted the position of $K_{e/k}$ from favoring enol (**A**, **B**, or **D**) to favoring keto (**I**, **J**, or **K**). Students observed the cumulative effects of aliphatic steric bulk or an aromatic electron-withdrawing group (that favors enol) and lone pair conjugation (that favors keto) in the values of $K_{e/k}$ for compounds **K** and **L**: in both cases, the lone-pair resonance effect trumped the other effects (**D** versus **A**; **K** versus **F**).

Evaluating Cumulative Effects

Nested in the study of the effect of lone pair conjugation on $K_{e/k}$ is an analysis of the accumulated effects of various structural elements on the position of equilibrium. From this panel of compounds, students were asked to consider and prioritize the effects of appending aliphatic, electron-withdrawing and electron-donating groups. They found in sets like **E**−**H** that R and R′ reinforced each other to favor strongly the enol form. Conversely, they found by comparing **A** and **I**, or **B** and **J**, or **D** and **K**, or **E**, **I**, and **L** that the keto form was favored in **I**−**L** as the resonance effect of the methoxy or ethoxy group negates the other effects.

Other Considerations

The $K_{e/k}$ values obtained by students were reproducible year-to-year and were consistent with previously reported values.[5] Students could prepare their own samples to investigate the effects of structure, analyte concentration, temperature, solvent, etc., as detailed in this paper and related papers in this *Journal*.[5] With 12 commercially available compounds, even in larger sections pairs of students ran one unique sample.

For the purposes of this experiment, we did not optimize concentration[5e] or relaxation time,[5l] although we commend

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J. Chem. Educ. XXXX, XXX, XXX−XXX

these approaches to faculty interested in focusing on these important features of NMR analysis. Our experimental parameters did not adversely affect these data; see the Supporting Information for further comment on the conditions used for this experiment.

CONCLUSION

A range of 1,3-dicarbonyl compounds was selected and vetted by several generations of students that expands the pool of compounds analyzed for enolization propensity using NMR. This pool of compounds, built on previous submissions to this *Journal*,[5] allowed students to investigate the phenomenon of structural effects including steric bulk, electron-withdrawing groups, and electron-donating groups, on the position of keto-enol equilibrium. This approach may be tailored by individual instructors to suit a variety of pedagogical formats (direct analysis, discovery, individual or group, etc.) for use at several levels of the undergraduate curriculum, including introductory and advanced organic chemistry, instrumental analysis, and physical chemistry.

Students, who were trained in a typical 1 sample = 1 analyte model, consistently reported that data from samples containing 2 analytes were more challenging to interpret. Over time, the lab manual (Supporting Information) was updated to provide students with more guidance in tabulating their data, an improvement students found helpful both in interpreting the data and in forming a better appreciation for the effect of structure on reactivity (as measured by position of equilibrium). While the students do not themselves perform the chemistry that converts the keto to the enol form, they uniformly reported fascination and interest in the first-hand evaluation of trends such as the effect of steric bulk, electron-withdrawing groups, and electron-donating groups on the chemistry of these systems. They carried this interest into later parts of the semester in which they demonstrated facility in describing such trends in other chemical reactions. In summary, with careful compound selection by an instructor, or perhaps by students themselves, students could investigate various effects of structure on $K_{e/k}$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00170.

Instructor's Notes and the Student Laboratory Manual (PDF, DOCX)

Keto−enol spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: chamann@albright.edu.

Present Address

[†]Department of Chemistry, Muhlenberg College, Allentown, Pennsylvania 18104, United States.

Notes

The authors declare no competing financial interest.

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