

# Keto–Enol Tautomerization of Acetylacetone in Mixed Solvents by NMR Spectroscopy. A Physical Chemistry Experiment on the Application of the Onsager–Kirkwood Model for Solvation Thermodynamics

Candice H. Courtney and V. V. Krishnan\*



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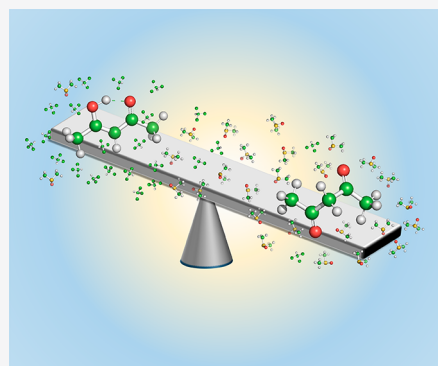
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Supporting Information

**ABSTRACT:** Keto–enol tautomerism is a fundamental concept that examines the migration of a proton between two constitutional isomers, the keto and enol tautomer. Many experiments have been proposed to understand the concept behind Meyer's Rule, which states that the keto tautomer is favored as the solvent polarity increases. However, all the experiments have only been performed in a single solvent. A new physical chemistry experiment is introduced to determine tautomerization equilibrium in binary solvent mixtures using nuclear magnetic resonance (NMR) spectroscopy, by systematically varying the molar ratio of the solvents. This approach allows the students to explore the variation of the polarity of the solvent system as a continuous variable. Furthermore, using an empirical method, the solvent polarity at any binary solvent condition can be converted to an effective dielectric constant of the sample. Because of this ability, the keto–enol tautomerization equilibrium constant can be directly related to the solvation Gibbs energy using the Onsager–Kirkwood theory. Detailed experimental procedures for the direct adaptation of the experiment using a high-resolution or desktop NMR spectrometer is provided in the Supporting Information.

**KEYWORDS:** Upper-Division Undergraduate, Graduate Education/Research, Physical Chemistry Laboratory Instruction, Equilibrium, NMR Spectroscopy, Thermodynamics, Undergraduate Research



## INTRODUCTION

With the first introduction of keto–enol tautomerism equilibrium by Ward in this *Journal* more than 50 years ago,<sup>1</sup> it has been a valuable experiment adopted by many undergraduate educators. Since the concept of keto–enol tautomerism equilibrium is such a fundamental phenomenon in many areas of chemistry, a range of applications has been introduced as laboratory experiments in both physical and physical–organic chemistry laboratories. Among them, many notable publications utilize nuclear magnetic resonance (NMR) as a means to follow the equilibrium process.<sup>2–16</sup> Advanced experimental procedures have been developed to address kinetic and thermodynamic concepts<sup>10,12</sup> of keto–enol tautomerism. In particular, Cook and Feltman introduced the importance of solvent effects,<sup>9,11</sup> and more recently Sandusky<sup>15</sup> expanded the approach in the context of the Onsager–Kirkwood theory, thus directly relating to the classic Meyer's Rule established more than a century ago.

The foundation of this work started when Kurt Meyer studied the bromination of the enol tautomer in the presence of a single solvent. Through titration, he was able to determine the percentage of enol tautomer present in the mixture. From his work, he concluded that as the solvent's polarity increased,

the keto tautomer was favored. This would later be known as Meyer's Rule and is referred to often in the literature.<sup>17</sup> To understand how a change of the solvent polarity alters the keto–enol tautomerization equilibrium constant ( $K_T$ ), naturally, the experiments are repeated in a set of solvents of different polarities. Though the advantage of this approach allows for the expansion of the experiments to increase the pedagogical value, single solvent experiments measure keto–enol equilibrium only at the extreme values represented by the solvent and fail to capture how the equilibrium is altered continuously as the solvent polarity changes.

This work further takes advantage of the empirical tools available for the estimation of the dielectric constant of a solvent mixture,<sup>18,19</sup> and thus relates the change in the  $K_T$  directly with solvent polarity using the Onsager–Kirkwood theory.<sup>15</sup> This theory describes how the polarizability of a molecule is affected by the polarity of the solvent. In this paper,

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chloroform-*d* and dimethyl sulfoxide-*d*<sub>6</sub> (DMSO-*d*<sub>6</sub>), being miscible, were chosen to showcase a significant difference between dielectric constants, thus elucidating how the  $K_T$  changes as the molar ratios of the binary solvent mixture are varied. Finally, the estimated dielectric constant of the mixture can further be used to calculate empirically the change in the solvation energy between the keto and enol tautomers.

This paper will reflect how the keto–enol tautomerization equilibrium ( $K_T$ ) is affected when acetylacetone is in the presence of two solvents at varying molar ratios. This, in turn, will not only showcase the effects of solvent polarity at the extreme ends, in the case of acetylacetone in the presence of a single solvent but also get a glimpse into how the dynamics between the tautomers change as a function of a solvent's molar ratio.

## ■ LEARNING OUTCOMES FOR STUDENTS

Here we provide a concise description of this approach that can be quickly adopted in an undergraduate physical chemistry laboratory for upper-level physical chemistry students, or possibly upper level advanced organic chemistry students. Students should have basic knowledge of using and interpreting standard one-dimensional NMR spectra. The learning objectives of this experiment in an undergraduate physical laboratory are as follows:

- understand the quantitative nature of NMR spectroscopy and how a change in sample conditions can directly alter the spectral data
- learn the basics of optimizing an NMR experiment, quantify the peak intensities to molecular concentrations, combining multiple spectral data sets, and apply numerical methods such as nonlinear curve-fitting
- identify how solvents' polarity affects the keto–enol tautomerization equilibrium in a binary solvent mixture using NMR spectroscopy
- implement the use of mole fractions, both experimentally and empirically, to determine the dielectric constant of the mixture
- incorporate the data collected into the Onsager–Kirkwood formalism to determine the change in solvation energy of the keto–enol tautomerization equilibrium
- learn the basic principles involved in solvation thermodynamics and estimation of Gibbs energy using nontraditional methods such as solution NMR spectroscopy

## ■ DESCRIPTION OF THE EXPERIMENT

### Sample Preparation

Acetylacetone was purchased from Sigma-Aldrich and used without any further purifications. The solvent chloroform-*d* (99.96 atom % D) was purchased from Sigma-Aldrich. Dimethyl sulfoxide (DMSO-*d*<sub>6</sub>) ((99.9 atom % D), containing 0.03% (v/v) TMS) was purchased from Arcos Organics in 0.75 mL ampules. All solvents were used without further purifications. Newly purchased, unopened ampules were used when preparing the samples, to minimize any contamination that may occur from moisture in the air. Caution must be exercised as dissolved water might alter the measured equilibrium constants. Tetramethylsilane (TMS) was used as a reference standard for NMR spectral analysis.

Samples (800  $\mu$ L) were prepared in 1.5 mL Eppendorf tubes. Acetylacetone was held at a constant mole fraction of 0.02 ( $\sim 0.3$  M), and the remaining 0.98-mole fraction was varied between the solvents. Table S1 (Supporting Information) shows the breakdown of the 0.98-mole fraction between the binary solvent mixtures, for a total of 15 samples. Also, TMS (40  $\mu$ L) was added as a reference standard for all samples. In the case of the solvent DMSO-*d*<sub>6</sub>, in which 0.03% of TMS was already present, 40  $\mu$ L of TMS was still added for consistency. From the total sample volume, an aliquot of 650  $\mu$ L was pipetted into a Wilmad high throughput NMR tube, capped, and wrapped with parafilm.

### Experimental Procedures

Data collection was performed using a Varian/Agilent VNMR-400 MHz NMR spectrometer, equipped with a One-NMR probe with a single axis (*z*-gradient) pulsed-field gradient and at a temperature of 30 °C. One-dimensional proton (<sup>1</sup>H) experiments were run on each sample. Before running the <sup>1</sup>H experiments, the 90° pulse width was calibrated. One-dimensional NMR experiments with a pulse-angle of 70° (Ernst angle) was used.<sup>20</sup> A total of eight transients were collected for each sample, with a relaxation delay of 4.0 s and 32,768 number of points. The total <sup>1</sup>H run time was 49 s for each sample, not including locking and shimming. <sup>1</sup>H spectra were processed and analyzed using MestReNova (version 12.0.3-21384).

### Estimation of the Dielectric Constant of the Solvent Mixture

In understanding the effects polarity has on the tautomerization equilibrium, the ability to calculate the dielectric constant of a mixture at various polarizable conditions can give a numerical range on how the equilibrium changes as the solvent's polarity changes. Amirjahed and Blake<sup>18</sup> derived an empirical expression that related the mole fractions, dielectric constants, and the volumes of the binary solvent mixture to estimate the overall dielectric constant of the mixture as follows.

$$\epsilon = \frac{aX_1 + bX_2}{cX_1 + dX_2} \quad (1)$$

where  $\epsilon$  is the net dielectric constant of the mixture, the subscript 1 represents the more polar solvent, subscript 2 represents the less polar solvent, and  $X$  is the mole fractions of the two solvents. The coefficients  $a$ ,  $b$ ,  $c$ , and  $d$  are further calculated by using the dielectric constant ( $D$ ) and volume ( $V$ ) of each of the solvents as follows.

$$a = V_1 \left( \frac{3D_1}{D_1 + 2} \right); \quad b = V_2 \left( \frac{3D_2}{D_2 + 2} \right); \\ c = V_1 \left( \frac{3}{D_1 + 2} \right); \quad d = V_2 \left( \frac{3}{D_2 + 2} \right) \quad (2)$$

For the solvents dimethyl sulfoxide and chloroform, a dielectric constant of 46.7 and 4.8 D were used,<sup>21</sup> respectively, and the effect of deuteration on the dielectric constants was not considered. It is important to note that this way of empirically calculating the dielectric constant of a mixture does not consider the polarity of AcAc, and hence it is essential to keep the concentration of the AcAc much lower than the solvent concentrations. For the solvent combination presented here,

Table S1 shows the estimated dielectric constant for each solvent combination.

### Data Analysis

NMR spectroscopy directly measures the relative amount of the keto and enol tautomers in the sample mixture that can be estimated by integrating the peak areas of the hydrogens at the  $\alpha$ -carbon in the proton ( $^1\text{H}$ ) NMR spectra, [enol], and [keto], respectively. Upon integration,  $K_T$  is calculated using

$$K_T = \frac{[\text{enol}]}{[\text{keto}]} = \frac{[\text{CH}]}{\frac{1}{2}[\text{CH}_2]} \quad (3)$$

The Onsager–Kirkwood theory,<sup>22,23</sup> has been being applied to this study to examine the solvent effects on the keto–enol tautomer equilibrium.<sup>15,24–28</sup> The Onsager–Kirkwood theory gives a comprehensive way of explaining the polarizability of a given molecule within a dielectric medium, which is represented by the Onsager–Kirkwood factor  $((\epsilon - 1)/(2\epsilon + 1))$ , where  $\epsilon$  is defined as the dielectric constant of the mixture, for this research.<sup>29</sup> Using this Onsager–Kirkwood factor, Mills et al. derived a relation to evaluate the solvation Gibbs energy ( $\Delta\Delta G^\circ$ ) of the tautomers of various compounds.<sup>29</sup> The equation was modified with the term  $k_{\text{HB}}$  to account for the hydrogen bonding acceptor and donor parameters,  $\alpha$  and  $\beta$ , proposed by Kamlet and Taft.<sup>30,31</sup> In addition,  $k_s$  represents the difference in the squared dipole moments of the keto and enol tautomer ( $\mu_e^2 - \mu_k^2$ ). Using the thermodynamic definition of the equilibrium constant and the experimental value of  $K_T$  (eq 3), a general expression for  $\Delta\Delta G^\circ$  can be given as

$$\Delta\Delta G^\circ = k_s \left( \frac{\epsilon - 1}{2\epsilon + 1} \right) + k_{\text{HB}} \quad (4)$$

Equation 4 presents a linear relationship between the polarity (in terms of the Onsager–Kirkwood factor) and the Gibbs energy of solvation and thus provides a model to interpret how the polarity of the solvent affects the polarization of the keto and enol tautomer.

### Hazards

There are no significant hazards associated with the preparation of the samples for this experiment. Since the volumes of the chemicals are relatively small, the chemical exposure is minimal compared to the exposure a student would have in an undergraduate organic chemistry lab. It is important to note that dimethyl sulfoxide- $d_6$ , chloroform- $d$ , and tetramethylsilane are volatile organic compounds, and it is recommended that the samples be prepared over ice to minimize evaporation. To reduce the exposure to the vapors of the volatile compounds, samples should be prepared under a fume hood.

### Implementation in Physical Chemistry Laboratory Curriculum

**Implementation.** The laboratory can be implemented using a standard high-resolution NMR spectrometer or a desktop NMR spectrometer. On the basis of the experiments performed at both instruments by the students, a detailed procedure is provided in the Supporting Information. The projects were performed by a group of three students one year and an individual student the following year. If done individually, sample preparation of the 3 sets of 15 samples (45 samples in total) would take one 3–4 h laboratory period. The next laboratory period would consist of running the

samples on a standard high-resolution NMR spectrometer. However, depending on the number of students in the class, the laboratory session could be divided into multiple groups, with each group performing the same experiment with different solvent combinations. The solvent combination and the number of mole ratios determine the number of samples.

On the basis of the experience, we recommend at least nine different mole fractions that include pure solvent conditions as samples #1 and #9. Following the institution's policy on NMR facility use, the one-dimensional NMR spectra can be collected. At our campus, the students performed their experiments as they are trained at the beginning of the laboratory session. Upon completing the experiments, the raw NMR spectra were transferred to a computer that runs the processing software (*MestReNova*).

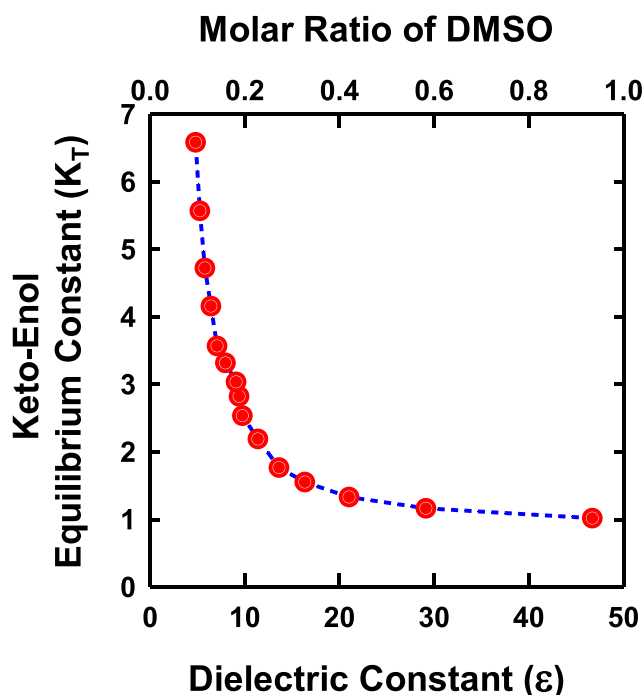
Each student created a master excel worksheet (see Table S1) that contains the details of the mole-ratio calculations, calculated peak values of the keto and enol resonances, the data fitting process, and summary of results. Data from all the students are shared, thus allowing the students to combine data from either replicated experiments with the same solvent combination or a different solvent condition. All the students submitted a formal report at the end of the experiment, and the learning objectives were used as a rubric to evaluate the written report. Students also submitted a copy of the excel worksheet for evaluations. All the reports were submitted online. Students with a focus on chemistry, biochemistry, or biophysical chemistry will learn the process for obtaining kinetic data, become familiar with statistical analysis through the use of algorithms, and achieve a deeper understanding of thermodynamic concepts through graphical and mathematical data analyses. The experiment and data analysis can be completed typically in an upper-level physical or biochemistry laboratory course within a period of 3 h. If the students are not able to complete the experiment within a laboratory period, *Parafilm* sealed samples can be stored under conditions to minimize solvent evaporation for a short period ( $\sim 1$  week).

In addition, the same experiments can be implemented in a desktop NMR spectrometer, instead of using a high-resolution NMR spectrometer. The details of the experimental procedure and student results are given in the Supporting Information.

## RESULTS AND DISCUSSION

The interpretation of the NMR spectra of AcAc in the binary solvent mixture is straightforward. Figure S1 shows the  $^1\text{H}$  NMR spectra of AcAc in either DMSO- $d_6$  or  $\text{CDCl}_3$ ; the chemical shifts of the enol proton ( $-\text{CH}$ ) appears at 5.48 ppm ( $\text{CDCl}_3$ ) and 5.69 ppm (DMSO- $d_6$ ), while the keto protons ( $-\text{CH}_2$ ) appear at 3.50 ppm ( $\text{CDCl}_3$ ) and 3.69 ppm (DMSO- $d_6$ ). Recall that Meyer's Rule states that as the solvent's polarity increases, the keto tautomer is favored, and correspondingly the value of the tautomerization equilibrium constant ( $K_T$ ) will be smaller than when the enol tautomer is favored (eq [3]). Figure 1 shows the change in  $K_T$  for the binary solvent mixture of DMSO and chloroform as a function of the mole fraction of DMSO, along with the estimated dielectric constant ( $\epsilon$ ) of the mixture (Table S1). Since DMSO is a more polar solvent than chloroform, for each solvent combination, as the mole fraction of DMSO increases, the value of  $K_T$  decreases. This indicates that the keto tautomer is favored and thus supports that Meyer's Rule can be applied to binary solvent mixtures. A small increase in the mole-fraction of DMSO at the initial part of the curve has a larger change in the measured  $K_T$  value. The



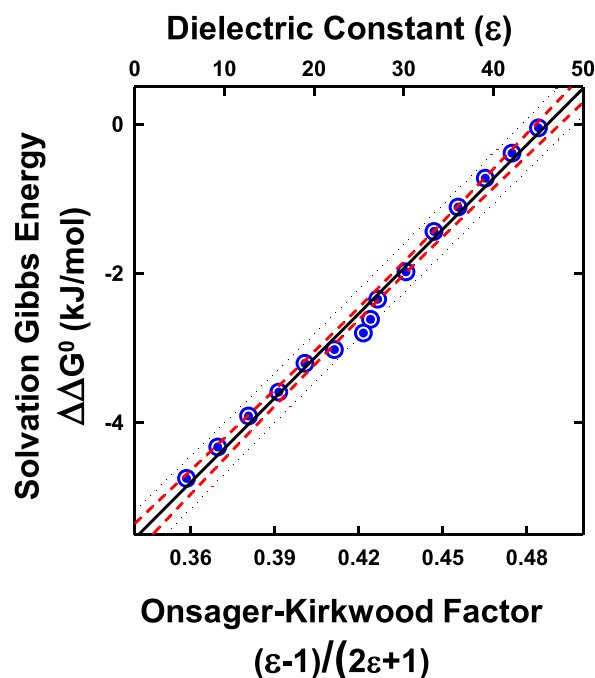


**Figure 1.** Keto–enol equilibrium as a function of increasing solvent polarity. Experimental values of keto–enol equilibrium constant ( $K_T$ ) are plotted as a function of the dielectric constant of the solvent mixture ( $\epsilon$ ). The solvent mixture is made of chloroform and dimethyl sulfoxide (DMSO). The second X-axis on the top shows the molar ratio of DMSO. The dashed blue line connects the experimental points.

solvent combination of DMSO and chloroform has a more substantial dielectric constant difference, 41.9, between the two solvents and appears to show an exponential trend between the mole fraction and  $K_T$  (Figure 1). Consequently, the higher is the shift in polarity of the solvent, the more drastic is the effect on the  $K_T$ .

Considering that the solvent's polarity influences the  $K_T$ , finding a way to calculate the polarity or the dielectric constant of a mixture ( $\epsilon$ ) is of interest. Herein, in the absence of availability of the experimental values of the dielectric constant of the mixture, it was estimated using an empirical method.<sup>18</sup> Though the use of empirical estimates is not the best option, it allows the exploration of the concept of continuous change in the polarity of the solvent. Furthermore, these approaches have an overall average percentage deviation between the estimated experimental values at less than 2%.<sup>19,32</sup>

At relatively low concentrations of the solute, the estimated dielectric constant of the solution can be related to the difference between the individual dipole moments of the keto and enol forms via the Onsager–Kirkwood theory. Figure 2 shows the relationship between the Onsager–Kirkwood factor  $((\epsilon - 1)/(2\epsilon + 1))$  to the solvation Gibbs energy ( $\Delta\Delta G^\circ$ ) of the keto and enol tautomers. The nonlinear least-squares fit of the experimental points (blue symbols) using eq 4 yields a slope ( $k_s = 37.72 \pm 1.02$  kJ/mol) and an intercept ( $k_{HB} = -18.38 \pm 0.43$  kJ/mol). Experiments performed using a second solvent combination of acetonitrile and chloroform using the same procedure yielded similar results ( $k_s = 33.38 \pm 1.59$  kJ/mol and  $k_{HB} = -16.51 \pm 0.66$  kJ/mol, data not shown).<sup>33</sup> In a study exclusively with nonpolar solvents,



**Figure 2.** Onsager–Kirkwood model applied to keto–enol tautomeric equilibrium. Onsager–Kirkwood factor  $((\epsilon - 1)/(2\epsilon + 1))$  shows a linear relationship between the solvation energy ( $\Delta\Delta G^\circ$ ). The corresponding dielectric constant of the mixture is also shown along the second X-axis on the top. Nonlinear least-squares fit of the experimental points (blue symbols) yields a  $k_s$  of  $37.72 \pm 1.02$  kJ/mol and a  $k_{HB}$  value of  $-18.38 \pm 0.43$  kJ/mol (see eq 4). The solid black line represents the best fit line, the dashed red line represents the 95% confidence interval, and the dotted red line represents the 95% prediction.

Powling and Bernstein reported a  $k_s$  value of 2.4 kcal/mol (10.0 kJ/mol).<sup>26</sup>

In a recent work published in this journal, Sandusky demonstrated the utility of the Onsager–Kirkwood theory to elucidate the solvent-induced changes in  $K_T$ .<sup>15</sup> This study reported a linear correlation between the net dipole moment of the single solvent ( $R^2 = 0.94$ ), while such a correlation was slightly curved concerning the Onsager–Kirkwood factor ( $R^2 = 0.88$ ). In both the correlations, the author reported that the solvent DMSO is an outlier.

Changing the molar ratio of the two solvents, from a dielectric constant of 4.8 (chloroform) and 48.7 (dimethyl sulfoxide), alters the effective dipole moment from 1.05 to 3.96 D.<sup>21</sup> Therefore, solvent conditions with a smaller net dipole moment stabilize the enol form relative to the keto form and thus would increase the  $\Delta\Delta G^\circ$  for the keto–enol tautomerization equilibrium. Following the conclusions of Sandusky,<sup>15</sup> the Onsager–Kirkwood model is highly suitable to quantitatively understand the role of polarity in the keto–enol tautomerism of AcAc. The linear relation between the  $\Delta\Delta G^\circ$  and the Onsager–Kirkwood factor further suggests that the shift in the equilibrium arises due to relative stabilization between the dipoles of the keto or enol concerning the net solvent dipole. Though the current work addresses the utility of the Onsager–Kirkwood theory, it differs from the previous notably in the experimental design that allows the students to measure  $K_T$  at any particular polarity within the boundary of the dielectric constants of binary solvents.

## CONCLUSIONS

The keto–enol tautomerization equilibrium constant ( $K_T$ ) of acetylacetone (AcAc) was shown to be significantly influenced by solvent polarity. This research further highlighted how the keto–enol tautomerization equilibrium is affected by solvent polarity by using a range of binary solvent mixtures, instead of only focusing on the extreme ends of solvent polarity. By using different solvent combinations of solvents with varying dielectric constants, it was shown that Meyer's Rule expanded to include binary solvent mixtures. This can be supported by both graphical and NMR (82 or 400 MHz) data, showing that as the solvent's polarity decreases, the keto tautomer is less favored, thus decreasing the tautomerization equilibrium. Besides, NMR (400 MHz) data from undergraduate students also supported Meyer's Rule, and students were able to discuss the effects that solvent polarity has on the tautomerization equilibrium constant of acetylacetone in binary solvent mixtures.

These experiments provide an opportunity to design and develop computational exercises that include implicit solvent models. The thermodynamics aspect of the experiment may also be expanded further by using variable-temperature measurements, measurement of dynamic parameters such as spin–lattice relaxation time of the nuclear spins ( $T_1$ ), and self-diffusion coefficients, as well as broader applications including other solvent combinations and other molecules that undergo the keto–enol tautomerization.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available at <https://pubs.acs.org/doi/10.1021/acs.jchemed.9b00737>.

Instructions for students for high-resolution NMR and desktop NMR spectrometers; NMR spectra of AcAc at 400 MHz and the chemical shift assignments; results for acetonitrile: chloroform mixture in desktop picoSpin80 spectrometer; summary of the results in a desktop picoSpin80 spectrometer (PDF, DOCX)

Calculation of dielectric constant of mixed solvents. All the calculations, including mole fraction determination, estimation of dielectric constant, Onsager–Kirkwood factor, and implementation of a linear fit to experimental data to calculate the solvation Gibbs energy, are given (XLSX)

## AUTHOR INFORMATION

### Corresponding Author

V. V. Krishnan – Department of Chemistry, California State University, Fresno, California 93740, United States; Department of Pathology and Laboratory Medicine, University of California Davis Medical Center, Davis, California 95616, United States; [orcid.org/0000-0002-0726-950X](https://orcid.org/0000-0002-0726-950X); Email: [krish@csufresno.edu](mailto:krish@csufresno.edu)

### Author

Candice H. Cortney – Department of Chemistry, California State University, Fresno, California 93740, United States

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acs.jchemed.9b00737>

## Notes

The authors declare no competing financial interest.

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