Project 3 – Keto-Enol Chemical Equilibrium & Kinetics

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OBJECTIVE: The ASU standard undergraduate physical chemistry courses, (i) elementary physical chemistry (CHM 341) and (ii) physical chemistry with a biological focus (BCH 341) primarily focus on (bio)chemical thermodynamics and kinetics. Project 3 in elementary physical chemistry laboratory (CHM 343) aims to complement the material in focuses 5 & 6 (chemical change and kinetics) of *Elements of Physical Chemistry*[1] through a combined computational, experimental and data science components. Specifically, students are asked to use computational and experimental techniques to acquire chemical equilibrium and kinetic data on keto-enol tautomerism in a dicarbonyl molecule(s) (e.g, acetylacetone). The primary objective is to use computational and experimental measurements to determine the molecular thermodynamic equilibrium and kinetics of keto-enol tautomerism under various solvent and/or temperature conditions. An emphasis is placed on both acquiring the computational and experimental data, as well as the data analysis required to make the relationship to molecular thermodynamic and kinetic theory. Furthermore, there is an emphasis in physical chemistry on quantitative data analysis, error analysis and the proper propagation of error through multi-step data analysis and calculations. Students will be evaluated through their write-up of project reports which should take on the style used by scientific manuscripts. The written reports will be evaluated using an anonymous peer-review system.

INTRODUCTION

The influence of solvents on chemical equilibria was discovered in the late 1800's and in the same period that keto-enol tautomerism was discovered.[1] The study of keto-enol tautomerism is a classic physical organic chemistry experiment. The most commonly used β-diketone for university level laboratory experiments is acetylacetone (AcAc) in combination with proton (^{1}H) NMR for direct quantification of the enol and keto molecular forms.[2] NMR is a viable method for measuring this equilibrium because the tautomeric equilibrium is slow on the NMR timescale and the keto-enol proton environments are well separated in their chemical shift.[3,4]

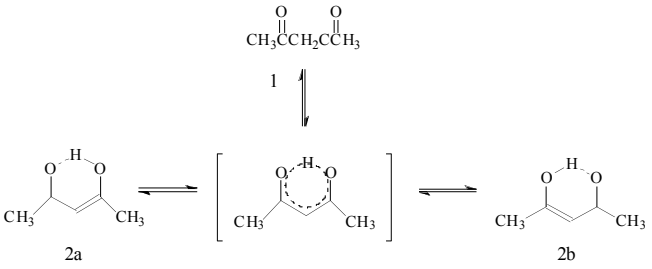
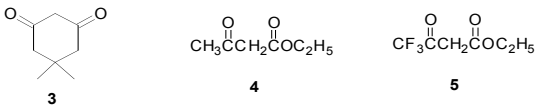


Figure 1 – Molecular schematic for the keto-enol equilibrium in 2,4 pentanedione, commonly referred to as acetylacetone (AcAc). The enol has two conformation, 2a and 2b, which incorporate an intramolecular hydrogen bond and typically interchange much faster than the NMR experimental time scale, leading to a single set of NMR signals for structure '2'. Stucture '1' is the diketone form (keto) and undergoes a slow exchange with the enol form.

It has been found that β-diketones typically have a shift in the tautomeric equilibrium toward the keto form with increasing solvent polarity. The implicit rationale for this observation is that the keto form is more polar than the enol form and hence is more stable in polar solvents. However, the concept that the keto form is more polar than the enol form is questionable.[5] Theoretical calculations and some experiments show that the keto tautomer of acetylacetone has a lower dipole moment than the enol tautomer in both the gas and solution phase.[6,7] Hence, students will do their own computational and remote laboratory experiments that allow them to come to your own conclusions about the effect of solvent on β-diketones keto-enol equilibrium and determine whether any measurable trends in solvent character can be correlated with experimental results.

Tautomerism is an especially important equilibrium in 1,3-dicarbonyl compounds. As represented in figure 1 for AcAc, there are two equilibria taking place, namely keto(1)-enol and enol(2a)-enol(2b). The enol-enol equilibrium is very fast on an NMR time scale and hence cannot be measured using NMR. However, the keto-enol equilibrium is slow on an NMR time scale and so can be measured using proton (^{1}H) NMR. We will be doing this with one or more 1,3-dicarbonyl compounds in various solvents. Figures 1 and 2 shows molecular structures of several dicarbonyl compounds that can be used include acetyl acetone (1), dimedone (3), ethyl acetoacetate (4) and ethyl 4,4,4-trifluoroacetate (5). From NMR experiments, students will explore the nature of solvent effects on tautomeric equilibria and how the interplay of polarity, hydrogen bonding ability, enthalpy and entropy of both solute and solvent are involved. NMR measurements can also be done as several temperatures to make a direct connection to thermodynamic energies (e.g., changes in enthalpy and entropy). Also, the time dependence after a change in temperature can provide chemical kinetics for the enol-keto 'reaction'.

NMR spectroscopy has a wide applicability to a diverse array of molecular and biological studies.[8,9] Chemists and



3 4 5

Figure 2 – Molecular structure of dimedone (3), ethyl acetoacetate (4) and ethyl 4,4,4-trifluoroacetate (5).

biochemists routinely use NMR to characterize synthesized materials. However, NMR can be used to provide much more detail than just the molecular structure of small organic and organometallic complexes. It can also be used for connectivity, spatial and dynamic information about a wide variety of materials. There are many books that describe the basics of NMR spectroscopy and hence we will not go into much detail in this introductory section.[1]

In this laboratory 'cloud' project, students will be introduced to NMR spectroscopy and collect ^{1}H NMR data on one or more β-diketone molecular compounds dissolved in several different (deuterated) solvents. The common slow equilibrium between enol and keto forms allows NMR to resolved and quantified both forms. This can be then be looked at as a function of temperature and both the kinetics and thermodynamic equilibrium can be determined.[10] Also, this is often done in several different solvents to determine the solvent effect on the tautomer equilibrium.[3]

On a modern NMR spectrometer, the methyl's (enol and keto forms), methylene and vinylic protons have resolved chemical shifts. Hence, these resonances can be used to determine the amount of enol versus keto tautomers in each solution. The concentration ratio of enol:keto is related to the equilibrium constant:

$$K_e = \frac{\%\ enol}{\%\ keto}$$

The equilibrium constant is dependent on the solvent and the temperature. The dependence of equilibrium on the solvent is discussed above and is related to the solvent dielectric constant versus the tautomer polarity stability. While the equilibrium constants dependence on temperature is related to the equilibrium reaction change in enthalpy (ΔH) and change in entropy (ΔS). By plotting ln K as a function of 1/T, students can construct a van't Hoff plot and determine ΔH and ΔS. This is discussed in all introductory physical chemistry textbooks and relies on the relation:

$$\ln K = -\frac{\Delta_r H^o}{RT} + \frac{\Delta_r S^o}{R}$$

where K is the equilibrium constant for a given reaction, R is the gas constant, T is the temperature, $\Delta_r H^o$ is the standard state change in enthalpy and $\Delta_r S^o$ is the standard state change in entropy for a given reaction.[1]

Extended-basis *ab initio* calculations with inclusion of polarization functions provide good results for the computational study of diketone tautomers.[6] The intramolecular proton transfer bonding and mechanism can be thoroughly explored using standard electronic structure computational chemistry applications such as Gaussian, Gamess, NWChem, Quantum Espesso and numerous other standard and open source quantum chemistry packages.[11] So, this is where students will start this project, with some computational 'experiments' to be able to make some initial predictions for the experimental NMR measurements that will be available for remote access to an autosampler NMR with all the necessary samples in place for remote collection of NMR experimental data.

PCHEM 'CLOUD' LABORATORY

Computational

Computational 'experiments' will be made using *ab initio* electronic structure computation package such as Molecalc (browser), GAMESS, or Gaussian.[12] Students are welcome to use any *ab initio* electronic structure computation programs. Gaussian is provided to students through ASU computing services (specifically, accounts and computer time on the ASU computer cluster called Agave, https://login.rc.asu.edu and a UI interface is available through WebMO). The primary objective of the computational component is to determine the keto-enol equilibrium that will be experimentally measured in the following lab periods (week 2). An outline of the general computational procedure is provided below:

- Using WebMO in combination with Gaussian '16 or some other common *ab-initio* molecular modeling programs (GAMESS, Spartan, etc.) for computational analysis of the keto-enol equilibrium.
  - Using a semi-empirical method (e.g. AM1), determine the energies and dipole moments of the keto and enol tautomers of acetyl acetone by optimizing their energies.
  - Using semi-empirical or Hartree-Fock method, determine the energy and dipole moment of the keto tautomer of acetyl acetone with the carbonyl plane-carbonyl plane dihedral angle fixed at zero degrees.
  - Use hybrid functional B3LYP/6-31-G* *ab initio* program to obtain gas phase energy of both keto and enol tautomers for your molecule. Minimize the energies to give the gas phase values for all the tautomers. It is recommended that students make a table for their project report that summarizes the energies, dipole moments and carbonyl plane-carbonyl plane dihedral angles (for the keto tautomer).
  - Use B3LYP/6-31-G* or HF/6-311-G** *ab initio* program to obtain the effect of solvation on the energy and/or keto-enol equilibrium. Solvation can be included in *ab initio* calculations using continuum models (e.g., SMD, CPCM, SCRF). Hence, this computational determined effect of solvation can be compared to the effect of solvent determined from experiment (NMR). WARNING: Because of the unusual properties of water, it rarely follows the trend that most organic solvents follow. Keep this in mind when doing calculations.

- Computational chemistry is commonly used before most experimental physical chemistry laboratory measurements. It is highly encouraged to use computational results to make predictions about experiments BEFORE they are done. For example, from the computational chemistry performed initially, make a prediction about how the enol-keto equilibrium will shift in various solvents experimentally via NMR experiments.

EXPERIMENTAL

Quantitative measurements of the enol and keto molecular conformations will be made using a remotely accessible NMR spectrometer. The operating instructions for the NMR spectrometer will be provided in separate documents or links. The general procedure is outlined below:

- A remotely accessible modern fully automated NMR spectrometer will be made accessible to students for several days of 24/7 instrument time. Details on remote access and basic remote experimental setup will be provided to students for the specific remote NMR instrument used on specific dates. Details will also be provided about the procedure to produce diketone solutions and will put the samples into a standard NMR tube, spinner and autosampler for students to remotely access for experiments (Samples will be provided and remotely accessible or students).
  - This is typically done with acetyl acetone and maybe one other di-ketone for study by the entire class. Prepare solutions of the chosen compound in 5 or more different solvents (C_6D_6, C_6D_{12}, CD_3CN, $CDCl_3$, acetone-d_6, dimethyl sulfoxide-d_6, etc) at a concentration of 1-100 mM. The solutions should be prepared directly in a standard 3 or 5 mm glass NMR tube with a total volume of ~0.6 or ~0.2 ml, respectively. This advanced preparation is necessary to allow equilibrium to be achieved. Also, a dilute solution is important to avoid dimer formation of the enol tautomers.
- NMR spectra can be acquired remotely by students. Students will have remote access to an automated NMR instrument for several days. Experiments can be setup and queued remotely for automated NMR experimental runs of any samples in the autosampler. There will be ample time for all students to remotely run the NMR spectrometer and remotely collected all necessary NMR data. The temperature dependence and solvent dependence of keto-enol equilibrium can both be explored. Modern NMR spectrometers are typically setup to automatically run experiments and upload the data to a shared cloud drive (e.g, www.spintropy.com).
- Once ^{1}H NMR is collected, data analysis will typically start with identifying signals for the enol vinyl proton and the keto methylene protons and integration of all the resonances. The enol vinyl proton signal typically appears in the δ=5-6 ppm region, and the keto methylene proton signal appears in the δ=3-4 ppm region. The methyl protons on both the enol and keto forms are also typically resolved and can be assigned.
- When running the NMR at elevated (or preferably lower) temperatures (typically between 273 and 353 K). Ensure that you stay well under the boiling point of the solvent. This is done so that the change in enthalpy and entropy can be calculated for the keto-enol reaction.
- Save all your ^{1}H NMR data in ascii format and in the standard Bruker format, so that you have data that can be analyze at home or in an ASU computer lab. The data processing can be done directly on the spectrometer. However, you should at minimum save the processed spectra and you should write down all the relevant processing parameters used to get the raw FID data into a spectral form. There are lots of free software packages for reading and processing Varian and Bruker NMR data.

DATA & ERROR ANALYSIS

An overview of the primary data analysis components for project 3 are provided below (all components should have associated error analysis).

- Plot all ^{1}H NMR spectra, assign all resonances and integrate all β-diketone resonances (peaks). This should include NMR spectra one or more β-diketones at several temperatures and in various solvents.
- Using the experimental NMR data, calculate the % enol tautomer present, the equilibrium constant, and the change in Gibb's free energy for each of the compounds in each of the solvents. Take into account the fact that there are two keto methylene protons for every single enol proton. Take the equilibrium as the following:

Some items to help with the project report:

Complete a table similar to the one shown below using your calculated results obtained from NMR proton data. Show how K and ΔG° were calculated in the supplementary information section.

Solvent	β-diketone		
	% Enol	K	ΔG° (kJ/mol)
$CDCl_3$			
DMSO			
Etc…			

Example Table

- Plot and record the keto and enol NMR proton chemical shift for each solvent and make a table of your results.
- Variable temperature NMR should be measured so that students can determine the equilibrium constant (k) at several different temperatures. This information can be used to determine the ΔH and ΔS for the equilibrium

reaction. Specifically, you can use a van't Hoff plot to determine that change in enthalpy and entropy for the reaction (equilibrium). The thermodynamics of a van't Hoff plot (equation) can be found in any standard physical chemistry textbook.

- Include the ΔG values for the equilibrium reaction in various solvents in the table shown above.
- Include *ab-initio* calculations in tabular and graphic format. Discuss your results and compare to experiment. Include solvation in your *ab-initio* calculations. An example dipole summary table:

Compound	**Energy (au)**		**Dipole (Debye)**		**Dicarbonyl Dihedral Angle (°)**
	Keto	Enol	Keto	Enol	
β-diketone					

- Include an estimate or calculation of error for every experimental and computational value. Perform a complete propagation of error analysis and include the detailed calculations in a supplementary section.

REFERENCES

(1) Atkins, P. W.; De Paula, J. *Elements of Physical Chemistry*, 7th ed.; Oxford University Press, USA, 2017.

(2) Drexler, E. J.; Field, K. W. An NMR Study of Keto-Enol Tautomerism in β-Dicarbonyl Compounds. *Journal of Chemical Education* **1976**, *53* (6), 392–393. https://doi.org/10.1021/ed053p392.

(3) Cook, G.; Feltman, P. M. Determination of Solvent Effects on Keto-Enol Equilibria of 1,3-Dicarbonyl Compounds Using NMR. Revisiting a Classic Physical Chemistry Experiment. *Journal of Chemical Education* **2007**, *84* (11), 1827–1829. https://doi.org/10.1021/ed084p1827.

(4) Cortney, C. H.; Krishnan, V. V. 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. *Journal of Chemical Education* **2020**, *97* (3), 825–830. https://doi.org/10.1021/acs.jchemed.9b00737.

(5) Iglesias, E. Application of Organized Microstructures to Study Keto-Enol Equilibrium of β-Dicarbonyl Compounds. *Current Organic Chemistry* **2004**, *8* (1), 1–24. https://doi.org/10.2174/1385272043486124.

(6) Buemi, G.; Gandolfo, C. Malondialdehyde and Acetylacetone. An AM1 Study of Their Molecular Structures and Keto-Enol Tautomerism. *Journal of the Chemical Society, Faraday Transactions 2: Molecular and Chemical Physics* **1989**, *85* (3), 215–227. https://doi.org/10.1039/F29898500215.

(7) Cusiter, M. A.; Le Fèvre, R. J. W.; Millar, D.; Pierens, R. K. Dipole Moments, Kerr Constants and Other Properties of Acetoacetic Ester and Acetylacetone. *Australian Journal of Chemistry* **1977**, *30* (3), 503–509. https://doi.org/10.1071/CH9770503.

(8) Akitt, J. W. *NMR and Chemistry: An Introduction to Modern NMR Spectroscopy, Fourth Edition*, 4th edition.; CRC Press: Boca Raton, 2017.

(9) Günther, H. *NMR Spectroscopy: Basic Principles, Concepts and Applications in Chemistry*, 3rd edition.; Wiley-VCH: Weinheim, 2013.

(10) Koudriavtsev, A. B.; Linert, W. Keto-Enol Equilibrium from NMR Data: A Closer Look at the Laboratory Experiment. *Journal of Chemical Education* **2009**, *86* (10), 1234–1237. https://doi.org/10.1021/ed086p1234.

(11) Sandler, I.; Harper, J. B.; Ho, J. Explanation of Substituent Effects on the Enolization of β-Diketones and β-Ketoesters. *Journal of Chemical Education* **2021**. https://doi.org/10.1021/acs.jchemed.0c01076.

(12) Cramer, C. J. *Essentials of Computational Chemistry*; Wiley: Chichester, 2004.