

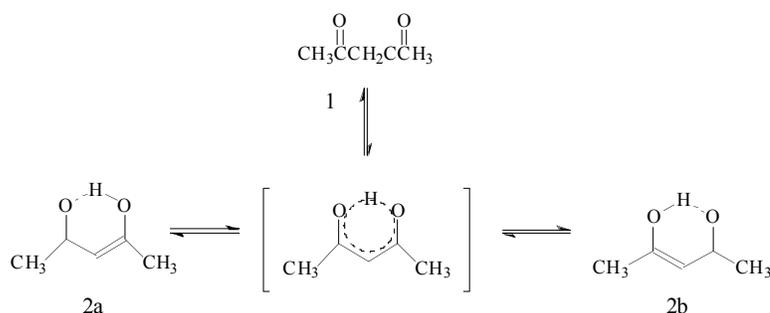
# EXPERIMENT 3 – Keto-Enol Equilibrium Using NMR

## Objective

Using proton NMR spectroscopy and computational analysis to evaluate the equilibrium composition of various keto-enol mixtures. Determine the effect of solvent and temperature on the keto-enol equilibria of one or more 1,3 dicarbonyl compounds. Use this information to determine the thermodynamic change (i.e.,  $\Delta G$ ,  $\Delta H$  and  $\Delta S$ ) for the keto-enol reaction and discuss the effect of solvent on the keto-enol equilibrium.

## 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 the keto-enol tautomerism of  $\beta$ -diketones and  $\beta$ -ketoesters is a classic physical chemistry experiment [2] and the first reported use of NMR keto-enol equilibria was by Reeves et al. [3]. The most commonly used  $\beta$ -diketone for these experiments is acetylacetone (acac) and use of proton NMR is a viable method for measuring this equilibrium because the tautomeric equilibrium is slow on the NMR timescale and the two proton environments are well separated in their chemical shift.



**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'. Structure '1' is the diketone form (keto) and undergoes a slow exchange with the enol form.

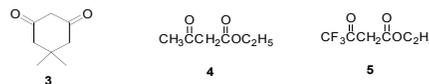
It has been found that  $\beta$ -diketones typically follow Meyer's rule of a shift in the tautomeric equilibrium toward the keto form with increasing solvent polarity [4]. The implicit rationale for this observation is that the keto form is more polar than the enol form and hence is more stable in polar solvents. However, the concept that the keto form is more polar than the enol form is questionable [5]. Theoretical calculations [6] and some experiments [7] show that the keto tautomer of acetylacetone has a lower dipole moment than the enol tautomer in both the gas and solution phase. Hence, your experiments will help you to come to your own conclusions about the effect of solvent on  $\beta$ -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. 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 ( $^1\text{H}$ ) NMR. We will be doing this with various 1,3-dicarbonyl compounds in several different solvents. Several dicarbonyl compounds that can be used include acetyl acetone (1), dimedone (3), ethyl acetoacetate (4) and ethyl 4,4,4-trifluoroacetate (5). From the NMR experiments, you will see how the nature of the solvent used affects the tautomeric equilibria and how the interplay of polarity, hydrogen bonding ability, enthalpy and entropy of both solute and solvent are involved.

### *Nuclear Magnet Resonance (NMR)*

Pulsed nuclear magnet resonance (NMR) spectroscopy has a wide applicability to a diverse array of molecular and biological studies. Chemists and 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 [8].



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

In this laboratory, we will introduce NMR in recitation and will get ‘hands-on’ training on a modern pulsed NMR spectrometer. We will collect standard  $^1\text{H}$  NMR data on a  $\beta$ -diketones compound dissolved in several different deuterated solvents. The deuteration is required to lock the frequency on a modern NMR spectrometer. This lock signal is then used to shim the sample in order to obtain the highest resolution spectrum possible (shimming eliminates magnetic field inhomogeneities in the sample). Once the sample is locked and shimmed, students can run a standard  $^1\text{H}$  NMR experiment and obtain a  $^1\text{H}$  spectrum at several different temperatures.

### *Chemical Equilibrium*

On a standard NMR instrument, the methylene and vinylic protons have well 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:

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

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 ( $\Delta H$ ) and change in entropy ( $\Delta S$ ). By plotting  $\ln K$  as a function of  $1/T$ , students can construct a van't Hoff plot and determine  $\Delta H$  and  $\Delta S$ . This is discussed in all introductory physical chemistry textbooks and relies on the relation:

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

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

## Experimental

1. Choose one of the  $\beta$ -diketones for study by the entire class. Prepare solutions of the chosen compound in at least four different solvents ( $C_6D_6$ ,  $C_6D_{12}$ ,  $CD_3CN$ ,  $H_2O/D_2O$ ,  $CDCl_3$ , acetone- $d_6$  and/or dimethyl sulfoxide- $d_6$ ) at a concentration of  $\sim 1$  mM. Prepare them at least 60 minutes in advance of running the proton NMR spectrum (to let the enol-keto ratio equilibrate). The solutions should be prepared directly in a standard 5 mm glass NMR tube with a total volume of  $\sim 0.7$ - $1.0$  ml. 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. Each of the solutions is prepared by a different group of students as assigned by the instructor.

2. A proton NMR spectrum is acquired for each of the solutions. A group of no more than three students may acquire the spectra together. The signals for the enol vinyl proton and the keto methylene protons are integrated for each of the spectra. The enol vinyl proton signal typically appears in the  $\delta=5$ - $6$  ppm region, and the keto methylene proton signal appears in the  $\delta=3$ - $4$  ppm region.

4. Repeat step #2 at 3 or more different temperatures (typically between 273 and 373 K). Ensure that you stay 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. (Temperature dependence only needs to be performed on one of the samples. Typically the DMSO sample)

3. Save all your  $^1H$  NMR data in ascii format and in the standard Varian/Bruker format, so that you have data that can be analyze at home or in PSH530 during the 2<sup>nd</sup> and 3<sup>rd</sup> week of 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.

4. The second and third weeks of this lab will be used to analyze data and carry out the molecular modeling calculations using Gaussian '09 or some other common *ab-initio* molecular modeling programs (GAMESS, Spartan, etc.).

a. Using a semi-empirical method (e.g. AM1), determine the energies and dipole moments of the keto and enol tautomers of your compound (e.g., acetyl acetone) by optimizing their energies.

b. Using semi-empirical or Hartree-Fock method, determine the energy and dipole moment of the keto tautomer of your compound (e.g., acetyl acetone) with the carbonyl plane-carbonyl plane dihedral angle fixed at zero degrees.

c. 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. Make a table that summarizes the energies, dipole moments and carbonyl plane-carbonyl plane dihedral angles (for the keto tautomer).

d. 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). Also, students can determine the effect of solvent on NMR spectra using Gaussian '09.

## Data Analysis

1. Plot all  $^1H$  NMR spectra, assign all resonances and integrate all  $\beta$ -diketone resonances (peaks).

2. Integrate all  $\beta$ -diketone resonances (peaks) for the variable temperature NMR data (and various solvents).

3. 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:



3. For your laboratory report:

a. Complete a table similar to the one shown below using your calculated results obtained from NMR proton data. Show how  $K$  and  $\Delta G^\circ$  were calculated in the appendix of your laboratory report.

Solvent	$\beta$ -diketone		
	% Enol	K	$\Delta G^\circ$ (kJ/mol)
CDCl <sub>3</sub>			
DMSO			
Etc...			

**Example Table**

- Record the keto and enol NMR proton chemical shift for each solvent and make a table of your results and/or show the NMR spectra.
- Variable temperature NMR was recorded so that you could determine the equilibrium constant ( $K$ ) at several different temperatures. This information can be used to determine the  $\Delta H$  and  $\Delta S$  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 [9].
- Include the  $\Delta G$  values for the equilibrium reaction in various solvents in the table shown in step a.
- 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 Moment (Debye)		Dicarbonyl Dihedral Angle ( $^\circ$ )
	Keto	Enol	Keto	Enol	
$\beta$ -diketone					

### Safety, Special Instructions, Tips, and Advice

- You must wear gloves and goggles when handling organic solvents and chemicals.
- NMR's have very large Magnetic Fields. You should not get near an NMR instrument with any metallic object on your person (e.g. watches, keys, etc.). Also, high magnetic fields are life threatening to people with pace makers.
- Look up the boiling point of all materials. NEVER take the NMR to a temperature that is close to the boiling point of the solvent.
- NMR tubes are thin-walled glass and are easily broken. Be very careful when handling these tubes and clean them before putting them in an NMR spectrometer.

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