

## NMR Determination of Keto-Enol Equilibrium Constants

### **Introduction**

In this experiment, you will learn about how modern NMR works to obtain usable spectra and use  $^1\text{H}$  NMR to determine the equilibrium composition of a keto-enol mixture. The key to the experiment will be the chemical shifts and spin-spin splitting patterns induced by the two different chemical forms.

### **Equipment**

Bruker AXR 500 MHz NMR with SGI workstation. The Bruker uses standard pulse methods and Fourier transform (FT) to acquire the spectral data.

### **Experimental**

#### *1. Introduction to the FT-NMR:*

- a. Prepare the following samples in NMR tubes:
  - i. Ethyl acetate in  $\text{CDCl}_3$
  - ii. Ethanol in  $\text{CDCl}_3$  ← note: use only 1 drop ( $1/2$  as much as suggested below).
  - iii. Toluene in  $\text{CDCl}_3$
- b. Fill the NMR tube to a height of ~4 cm with  $\text{CDCl}_3$  (“3-finger” level) and add 2 drops of the compound to be studied. Check to see if tetramethylsilane (TMS), which serves as an internal standard, has already been added to the solvent by the manufacturer or the TA. If not, add 1 drop of TMS to the tube. Put the cap on the tube and invert it several times to ensure mixing.
- c. Using the ethyl acetate sample and handout, lock & shim the NMR with supervision and acquire a  $^1\text{H}$  spectrum
  - i. If the peaks are broad, you may be badly shimmed or you need to dilute the sample
- d. Acquire a  $^1\text{H}$  spectrum of the ethanol under “standard” conditions. Plot the spectrum and integrate the signal.
- e. Investigate the following effects upon acquisition of data:
  - i. sweep width,
  - ii. movement of offset frequency,
  - iii. number of scans acquired, &
  - iv. receiver gain.
- f. Acquire the  $^1\text{H}$  spectrum of toluene

#### *2. Determination of keto-enol equilibrium constant:*

- a. Follow the experimental design in the Shoemaker handout for acetylacetone (2,4-pentanedione) and ethyl acetoacetate in 2 different solvents with the following exceptions:
  - i. Use  $\text{CDCl}_3$  and deuterated methanol as the 2 solvents.
  - ii. Make up four solutions - one of each compound in each solvent.
  - iii. Make the solutions to be 0.1 “mole fraction” compound in 0.7 mL of solvent.

Remember that “mole fraction of species  $a$ ” ( $X_a$ ) in a mixture of “ $n$ ” compounds is  $X_a = n_a / (n_a + n_b + n_c \dots + n_n)$  where the variable “ $n$ ” indicates *moles* of each species  $a, b, c, \dots, n$ , shown as subscripts. For one compound “ $a$ ” in a solvent “ $s$ ”, then  $X_a = n_a / (n_a + n_s)$ .

Needless to say, you will need to know something about the density and molecular weights of the materials you are working with.

- b. Acquire NMR spectra of the 4 solutions. Be sure to average enough spectra to obtain final spectra of sufficient signal to noise.

### **Questions**

1. What is a “FID”?
2. Why are sweep width and offset frequency important?
3. What pulse sequence did you use and why?
4. What is the purpose of acquiring more than one scan? How does acquiring 16 or 64 scans instead of 1 scan improve the spectrum?
5. If the field strength is 500 MHz and the coupling constant,  $J$ , of a doublet is 10 Hz, is the split peak resolved? What if  $J$  is 5 or 2 Hz?

### **Points to include in your lab report**

#### **Introduction:**

- Introduce topic of enolization of ketones and the possible equilibrium between the two forms.
- Raise the question as to how we could measure the keto-enol equilibrium in solution, which introduces NMR. Provide an introduction into why NMR is to be used in this experiment

#### **Experimental:**

- Include in your instrumentation description the important points about the instrument that directly affect the quality of the spectra you obtain (resolution, etc). You do not need to explain how an NMR works.
- Comment on the relationship of critical parameters, such as peak area, on the results that you wish to determine, e.g. the equilibrium constants.
- Describe how you collected your data with the NMR for each experiment.
- Define the solutions you prepared.
- Define how you are going to calculate the equilibrium constant, etc.

#### **Results:**

- Present as figures the spectra of each compound you measured. Identify each peak in each spectrum. Ideally you will include on each spectrum the chemical structure of the molecule(s) being measured and identify each peak to the hydrogens directly on the structure.
- Tabulate structural features, chemical shift, multiplicity, and peak areas (areas should round to integer multiples of the number of protons in each structural unit).
- Measure and report  $J$ -values for ethyl acetate.
- Do the same for the 2<sup>nd</sup> experiment where ethyl acetoacetate was measured.

- Calculate the equilibrium constants of tautomerism and fraction of the two compounds in keto and enol forms.
- Calculate  $\Delta G = -RT \ln(K_{eq})$ .

### **Discussion:**

- Comment on effects of varying NMR instrument parameters. Are there optimal settings? How does each parameter affect the final spectrum?
- Comment on the appearance of the peaks in the various spectra. Are they where you expect them to be based upon the literature? Are all hydrogen signals present and accounted for?
- Compare your experimental spectra with published spectra.
- Comment on the coupling constants (J) you measured and how they relate to the expected values.
- Do you see resolved split signals as expected? Is instrumental resolution able to resolve the multiple peaks? If not, do you believe the problem is related to your tuning and use of the instrument or is it a limitation of the instrument field strength?
- Do you get the expected integrations within compounds that are expected? If not, what are the exceptions? What might explain the exceptions?
- Compare the equilibrium constants and fraction of keto/enol to published data.
- Interpret the significance of the equilibrium constant. Why is one form favored?
- Comment on the effect of solvent on your results.

### **Handouts**

1. *CIL NMR solvent data chart*
2. D.P. Shoemaker, C.W. Garland, & J.W. Nibler, Experiment 44: NMR determination of keto-enol equilibrium constants, in *Experiments in Physical Chemistry*, 5<sup>th</sup> Ed, McGraw-Hill, NY, 1989, pp 522-531.
3. H.E. Gottlieb, V. Kotlyar & A. Nudelman: NMR chemical shifts of common laboratory solvents as trace impurities. *J. Org. Chem.* **62**: 7512-7515, 1997.
4. J.L. Burdett & M.T. Rogers, Keto-enol tautomerism in  $\beta$ -dicarbonyls studied by NMR spectroscopy. I. Proton chemical shifts and equilibrium constants of pure compounds, *J. Am. Chem. Soc.* **86**: 2105-9, 1964.
5. M.T. Rogers & J.L. Burdett, Keto-enol tautomerism in  $\beta$ -dicarbonyls studied by NMR spectroscopy. II. Solvent effects on proton chemical shifts and on equilibrium constants, *Can. J. Chem.* **43**: 1516-26, 1965.
6. R.M. Claramunt, C. Lopez, M.D.S. Maria, D. Sanz & J. Elguero: The use of NMR spectroscopy to study tautomerism. *Prog. Nucl. Magn. Reson. Spectrosc.* **49**: 169-206, 2006.

### **References**

1. D.A. Skoog, F.J. Holler & S.R. Crouch, *Principles of Instrumental Analysis*, 6<sup>th</sup> ed, 2007: Chap 19: Nuclear magnetic resonance spectroscopy.
2. R.M. Silverstein, G.C. Bassler, & T.C. Morrill, *Spectrometric Identification of Organic Compounds*, 4<sup>th</sup> ed. 1981, Chapter 4 pp. 181-197 (stopping at Protons on Nitrogen). Also helpful - pp. 220-222, 231, & 237 (on reserve in Cook Library).

3. Current edition is: R.M. Silverstein & F.X. Webster, *Spectrometric Identification of Organic Compounds*, 6<sup>th</sup> ed. 1998, Chapter 4.
4. R.S. Macomber, *A Complete Introduction to Modern NMR Spectroscopy*, 1998 (Baily-Howe: QD96.N8 M3 1998; on reserve in the Cook Library)
5. J.B. Lambert, H.F. Shurvell, D.A. Lightner, & R.G. Cooks, *Organic Structural Spectroscopy*, 1998, Chapters 2 & 3.

*Papers on FT-NMR in general:*

6. R.W. King & K.R. Williams, The Fourier-transform in chemistry - Part 1. Nuclear magnetic resonance: Introduction, *J. Chem. Ed.* **66**: A213-9 (1989).
7. R.W. King & K.R. Williams, The Fourier-transform in chemistry - Part 2. Nuclear magnetic resonance: The single pulse experiment, *J. Chem. Ed.* **66**: A243-8 (1989).
8. R.W. King & K.R. Williams, The Fourier-transform in chemistry - NMR: A glossary of NMR terms, *J. Chem. Ed.* **67**: A100-5 (1989).