

Studies in Configurational & Conformational Analysis

To obtain a complete understanding of the structure of compounds, studying the conformation and configuration of the molecule can be two of the more challenging and exciting topics. There have been many instrumental methods developed for studying stereoisomerism, particularly techniques designed to determine the absolute configuration, and the more stable conformations of various compounds. The configuration and conformation of a molecule can have far reaching effects in many areas of science, including medicinal chemistry, materials chemistry, biochemistry, and supramolecular chemistry, just to name a few.

One of the most versatile methods for studying the conformation and configuration of molecules takes advantage of the Nuclear Overhauser effect (NOE) in NMR spectroscopy. In short, NOE measurements allow one to determine which groups or atoms of a molecule are close spatially. While spin-spin coupling can be used to study the stereochemistry of atoms separated by 3, 4 or even 5 bonds, NOE allows for the study of groups which may be separated by countless bonds, but due to conformation are relatively close to one another in space. This technique is used extensively to study macromolecular conformations such as protein folding and small molecule binding to proteins.

Acetanilide offers a nice simple example of how NOEs can be used to determine configuration. The *cis* configuration of the amide has the N-H and CH₃ groups located relatively close in space, while the *trans* configuration should have the CH₃ and an aryl C-H group relatively close, see Figure 1. Thus, each configuration should have distinct NOEs, allowing one to use the NOE data to determine the predominant configuration of the amide.

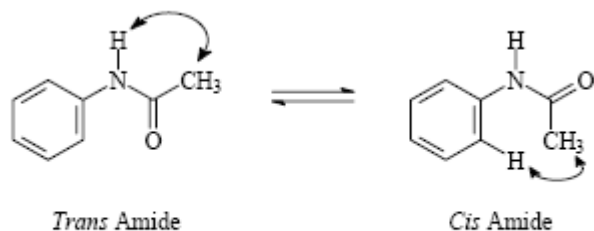


Figure 1. *Cis-Trans* equilibrium of acetanilide.
Expected NOEs are indicated with double-headed arrows.

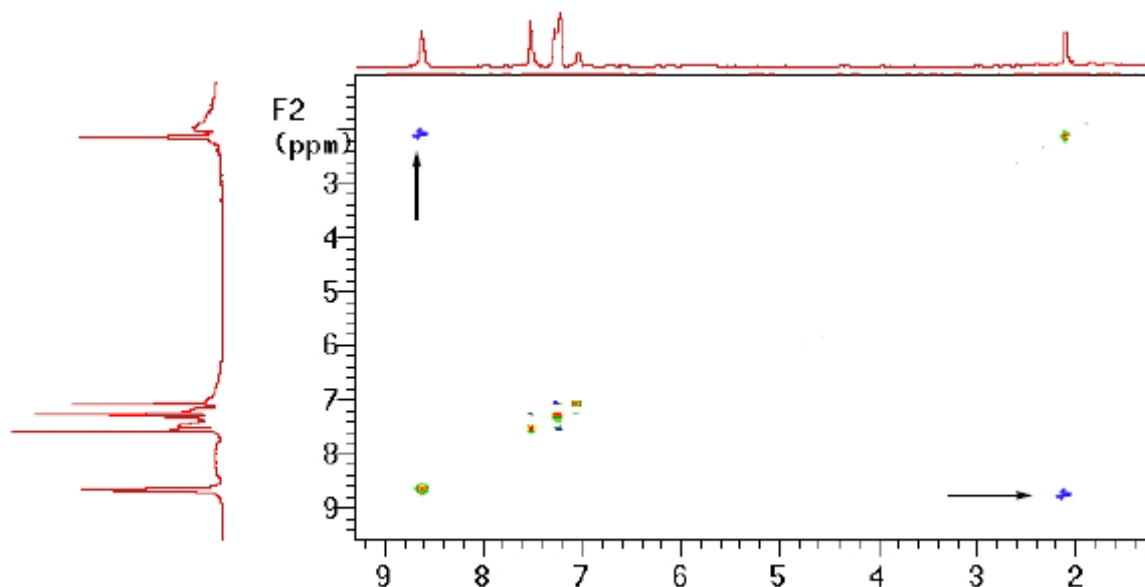


Figure 2. NOESY spectrum of acetanilide in CDCl_3 at 300 MHz. Arrows indicate the important NOE crosspeak.

In fact, the actual NOESY spectrum for acetanilide clearly shows an NOE between the amide N-H (~ 8.8 ppm) and the CH_3 group (~ 2.1 ppm) thus indicating that the *trans* conformation predominates, see Figure 2.

In this experiment, each student will prepare a compound that will be used to study both the configuration of a newly formed double bond (*E/Z*) and the conformation of the molecule, see Synthetic Scheme.. The molecule only has one-degree of rotational freedom, thus simplifying the study. Rotations about this single bond will be responsible for the *s-cis* and *s-trans* conformations, see Figure 3. Molecular mechanics calculations can be performed on the target compounds to determine the stability of the various isomers.

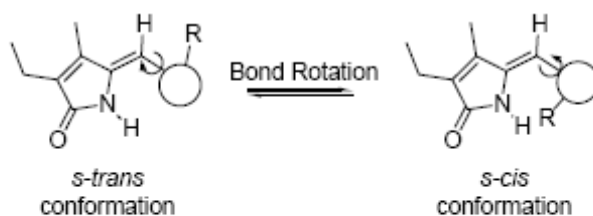
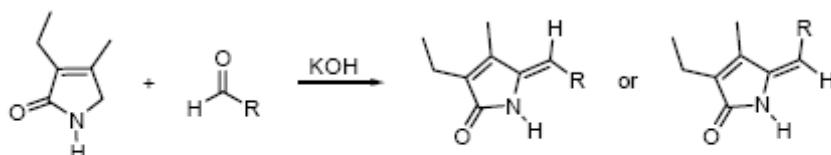


Figure 3. Schematic showing the bond rotation between the *s-cis* and *s-trans* conformations. The circles represent *ortho* substituted aryl groups.

Assignment:

- 1) Prepare two target compounds based on procedure below (aryl aldehydes will be provided by the instructor)
- 2) Determine the structure of the target compound using ^1H & ^{13}C NMR
- 3) Measure both the 1-D NOE and NOESY spectra for your target compound
- 4) Hypothesize the configuration of the double bond and the preferred conformation for your target compound and then compare with the experimental result.
- 6) Determine the mechanism of the reaction used to make your target compound
- 7) Perform a literature search to find examples that validate your results
- 8) Determine the theoretical and percent yield for your synthesis



Synthetic Scheme. Preparation of the target compounds showing the *E/Z* isomers. The *s-cis* and *s-trans* isomer are not indicated.

Experimental:

To a 50 mL RBF was added 0.125 g (1.0 mmole) of 3-ethyl-4-methylpyrrolin-2-one, 5 mL of 4 M KOH, and 10 mL of methanol. One molar equivalent of the desired aldehyde was added to the solution, and the reaction mixture was stirred at room temperature for 24 hours. After the reaction was complete, water was to bring the total volume to ~50 mL. The precipitate was collected by vacuum filtration and air dried to give the desired compound.

Additional Reading:

- (1) Neuhaus, D.; Williamson, M. P. *The nuclear Overhauser effect in structural and conformational analysis*; 2nd ed.; Wiley-VCH: New York, 2000.
- (2) Nelson, J. H. *Nuclear magnetic resonance spectroscopy*; Prentice Hall: Upper Saddle River, NJ, 2003.
- (3) Nakanishi, K. o. *One-dimensional and two-dimensional NMR spectra by modern pulse techniques*; Kodansha ; University Science Books: Tokyo Mill Valley, Calif., 1990.
- (4) Field, L. D.; Sternhell, S.; Kalman, J. R. *Organic structures from spectra*; 3rd ed.; J. Wiley & Sons: Chichester, West Sussex, England ; New York, 2003.
- (5) Hore, P. J.; Jones, J. A.; Wimperis, S. *NMR, the toolkit*; Oxford University Press: Oxford ; New York, 2000.
- (6) Beer, P. D.; Gale, P. A.; Smith, D. K. *Supramolecular chemistry*; Oxford University Press: Oxford ; New York, 1999.