Computational and Experimental Study of Isomerization in N,N-dimethylacetamide (DMA) and its Derivatives

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Abstract

In this investigation, we will examine the barrier of isomerization in N,N-dimethylacetamide (DMA) and some of its derivatives both experimentally (temperature dependent NMR) and computationally (with the WebMO interface to Gaussian 03). The NMR portion of lab will be done as a group while the computational part will be done individually (with the results pooled amongst the members of your group).

Related Readings

1. Wiberg, K. B., Breneman, C. M., *Resonance Interactions in Acyclic Systems. 3. Formamide Internal Rotation Revisited. Charge and Energy Redistribution along the C-N Bond Rotational Pathway*; JACS, **114**, 831-840 (1992).
2. Gasparro, F. P., Kolodny, N. H. *NMR Determination of the Rotational Barrier in N,N-dimethyl Acetamide* J Chem Ed, **54**, 258-261 (1977).

Background

In this investigation, we explore the kinetics of the hindered rotation about the C—N bond in N,N-dimethylacetamide (DMA). If DMA were a completely rigid molecule, it is expected that the amino methyl protons will exhibit two resonances integrating for three each in the proton NMR, corresponding to CH_3 groups that are "cis" and "trans" to the carbonyl group. If, on the other hand, there was free rotation about the C—N bond, then one would observe only one resonance as all six protons would have the same "average" chemical environment. In fact, DMA is an intermediate case, with two, slightly broadened resonances existing at room temperature. With increased temperature these resonances broaden and coalesce into a single transition. Our goal is to determine the activation barrier for the rotation about the C—N bond by measuring the rate of the isomerization as a function of temperature.

We will first study this system from a computational perspective trying to understand the relative energies of the different conformers and the electronic structure of these compounds and how this electronic structure influences the energetics of conformational isomerization. Concurrently we will examine the temperature dependent NMR spectrum to get a sense as to the relative population of these conformers and the barrier to isomerization. The computational and experimental results will be combined to develop a detailed understanding of this class of molecules and their 3D conformation. This study has increased relevance because the amide linkage in these systems is functionally identical to the peptide bond which connects amino acid residues to form large and biologically important proteins.

In preparation we will read two papers to determine previous experimental and computational approaches to this question.

Pre-Lab Exercises

1. Read the papers listed in the related readings section (sent to you via e-mail). Focus on the abstract and first few sections of the JACS paper.
2. Answer the following questions about the JACS paper:
    a. What do they find from their computations to be the barrier to isomerization?
    b. Why is it useful to look at the changes in C-N and C-O bond length upon isomerization?
3. Sketch the structure and an approximate proton NMR spectrum for N,N-dimethylacetamide.
4. Read and fully understand this lab handout; see Dr. Smith's website for further information. (Gain access from the main GAC Chemistry site.)

Note: Do #2 and #3 on a separate sheet; these will be collected in lab.

Procedure

General Information

- The experimentation and computation will span two weeks during which groups of ~three will spend about 2 hours recording temperature dependent NMR spectra and each member of the group will carry out extensive molecular modeling.
- Each group will record the temperature dependent proton NMR spectrum of either N,N-dimethylacetamide (DMA).
- We will do calculations using WebMO as a graphical Web-based front-end to Gaussian 03 to explore and understand the underlying electronic structure, relative energies of conformations, and other relevant comparisons using a variety of different model chemistries. Outline specific properties that you will examine but use the calculations to explore and understand the subtle differences between a series of compounds. Use the article by Wiberg and Breneman for ideas as to useful questions to explore. We will explore several aspects of 3-5 different derivatives including relative energies of conformers, the barrier to isomerization through relaxed potential energy scans, NBO (natural bond order) analysis yielding bond orders and atomic charges, and examination of molecular orbitals. Use the tools and the ideas developed to also examine a dipeptide and its conformational flexibility. Diglycine or dialanine might be reasonable starting points. The aim is to put together a fairly complete picture of the dynamics of isomerization in a range of these compounds and write out several paragraphs with tables providing an overview of the specific molecules and the trends you observe. Be creative in selecting some interesting derivatives to examine, they are free since they are just *in silico*! (See: Gustavus Computational Resources).

Experimental Investigation

- We will record the temperature dependent NMR spectrum for one of the compounds. (See Gustavus NMR tips)
- Ethylene Glycol will be used for temperature calibration.
- Use Mestrec to analyze your spectrum.
- For analysis of the data see Gasparro and Kolodny (i.e., the J Chem Ed paper).

- We will want to determine the activation energy for the isomerization process and compare this with the value computed below.
- Use the Mathcad document: NMR_Bloch.mcd to analyze the temperature dependent spectra and determine the most appropriate value of t at each temperature. Construct a plot to determine the activation energy for isomerization.

$$\tau = \frac{1}{2k}$$
$$k = A \cdot e^{-E_a/RT}$$

Arrhenius Equation

- Using regression E_a can be determined from the slope and A (the Arrhenius pre-exponential factor, the rate in absence of a barrier) can be determined. An example Mathcad document for the example of N,N-dimethylformamide is at: Mathcad: Kinetics of Isomerization in N,N-dimethylformamide, Matcad file: NMR_Temp_data.mcd

Computational Investigation

This investigation is self directed, but below are some details you may want to examine. You need to explore the barrier to isomerization to compare this to your experiment. The quantum chemical calculations are handled by WebMO as a front-end to Gaussian 03.

Quantum Chemical Calculations

- Draw N,N-dimethylacetamide, formamide, and/or methyl-formamide in WebMO
- Optimize and examine these structures within two different model chemistries (*ie.* AM1 or HF and 6-31G(d) or others).
- Compare the structures and record some pertinent geometrical data.
- Examine the energy associated with the barrier to isomerization using the potential energy function in WebMO with Gaussian 03.
- Carry out a "relaxed" potential energy scan to get at the barrier to isomerization. You can create a calculation that will scan the desired dihedral angle (the angle formed by four atoms with the first three defining a plan and the fourth forming an angle with the rest) to get energy versus angle, the potential energy. Use a *coordinate scan* type of calculation in WebMO with the computational model chemistry you are using (*ie.* AM1/3-21G or HF/6-31G(d)) and check preview input. Add the following line to the bottom of the text file when you preview input:

  3 4 5 6 20.0 S 40 10.0

- Leave a blank line and then enter the above with the ***3 4 5 6* representing the numbers of the atoms in the dihedral you are examining (you can get the atom numbering in the job window by clicking on the lowest icon on the left of the view window)**, the *20.0* representing the starting angle, the *S* indicates a scan, the 40 is the number of steps, and the 10.0 is the number of degrees increment in each step. This same strategy can be used to examine bond lengths and bond angles by specifying only 2 or 3 parameters, respectively. WebMO will

provide a link to a plot in the output file after the calculation completes. You can also save the x,y data from this plot to use in Excel or SigmaPlot through the menu above the plot.

- Examine the molecular orbitals (use appropriate calculation type in WebMO) and the charges on the atoms to gain insight into changes upon isomerization, the nature of the 90 degree (approximately the transition state structure). To get a 90 degree structure, take an optimized structure and use it as the basis of a new job, open the editor, select the 4 atoms making up the dihedral and then go to the adjust menu and set the dihedral to 90 degrees. The calculation should either be a energy calculation (not optimization) or for advanced users the "z-matrix" can be edited to fix this angle by changing the code in the WebMO z-matrix window from an O to a F (for fixed) next to the proper combination of for atoms (dihedral).
- See further computational approaches for maximum insight development…: Computational Investigation of Dimethylacetamide derivatives

Report/Analysis

Write the report as a group in the form of a communication (you can use the JACS paper as another source of formatting tips). Determine the best way to present all of your results (NMR and computational) in a clear and concise manner. For the discussion section, prepare a three or more paragraph discussion of the combined results with an attempt to maximize insights gained from experiment, computation, and the literature results. Also discuss detail any conclusions that can be drawn from your calculations and compare them to the higher level calculations and results presented in the above paper. A nice addition would be a comparison to the values in Table 2 of Gasparro and Kolodny (see McQuarrie and Simon pages 1167-1168 to determine how to calculate these values).

References

1. Wiberg, K. B., Breneman, C. M., *Resonance Interactions in Acyclic Systems. 3. Formamide Internal Rotation Revisited. Charge and Energy Redistribution along the C-N Bond Rotational Pathway*; JACS, **114**, 831-840 (1992).
2. Gasparro, F. P., Kolodny, N. H. *NMR Determination of the Rotational Barrier in N,N-dimethyl Acetamide* J Chem Ed, **54**, 258-261 (1977).