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

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).
3. McQuarrie and Simon, Chapter 28.

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
See pre-lab worksheet (on website).

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 N,N-dimethylacetamide (DMA). You will likely only be able to record data at 3 or 4 temperatures per group so two groups will share the data from the full temperature range.
- Each member of the group will conduct extensive molecular modeling on one amide molecule. The exact calculations will be discussed below.

Experimental Investigation

- We will record the temperature dependent NMR spectrum for one of the compounds. (See Gustavus NMR tips) There is a separate handout with the NMR instructions and another handout on how to use ftp and MestreC to analyze the data.
- Ethylene Glycol will be used for temperature calibration. The NMR shift of the two peaks in ethylene glycol is known as a function of temperature (in Hz). The list of these shifts is on the website or available in a book next to the NMR. Using the shifts you measure, estimate the actual temperature in the NMR – *you can not use the temperature reading on the NMR!*
- Use MestreC to analyze your spectrum. After converting the FID to a spectra and doing the appropriate manipulations (as outlined in the MestreC instruction handout), you'll need to save your data as an ASCII file. Instructions to do this can be found in "NMR Spectra Fitting Instructions.pdf" on the website.
- We will do an analysis similar to Gasparro and Kolodny (i.e., the J Chem Ed paper on the website). By using the "NMR Spectra Fitting Instructions.pdf" and the "NMR Spectra Fitting.xls" file, find the values of τ and K at each temperature. (The fitting routine fits g(υ) from Equation 4 of Gasparro and Kolodny to your spectra.) Be sure to adjust υ_A and υ_B for each temperature!
- Recall that

$$\tau = \frac{1}{2k}$$

  and find the rate constant.
- Using the techniques learned from the SN2 lab, find the activation energy and pre-factor for the isomerization process. You will be able to compare this value to the values you tabulated in the pre-lab.

$$k = A \cdot e^{-E_a/RT}$$ Arrhenius Equation

- Use transition state theory (the equations from Ch 28 as described in the prelab) to find $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$. Note that because our reaction is an isomerization,

$$E_a = RT + \Delta H^{\ddagger}$$

Computational Investigation

Part of this investigation is self directed (i.e., you can choose to explore different parameters and ideas related to these amides), but I will list a few things below that you are expected to calculate. 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. We will examine a series of amides to understand the subtle differences between a series of compounds. We will explore several aspects of 3-5 different derivatives including relative energies of conformers, the barrier to isomerization through relaxed potential energy scans, and NBO (natural bond order) analysis yielding bond orders and atomic charges. Be creative in selecting some interesting derivatives to examine, they are free since they are just *in silico*! Use the article by Wiberg and Breneman for ideas as to useful questions to explore. 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.

You need to explore the barrier to isomerization to compare this to your experiment

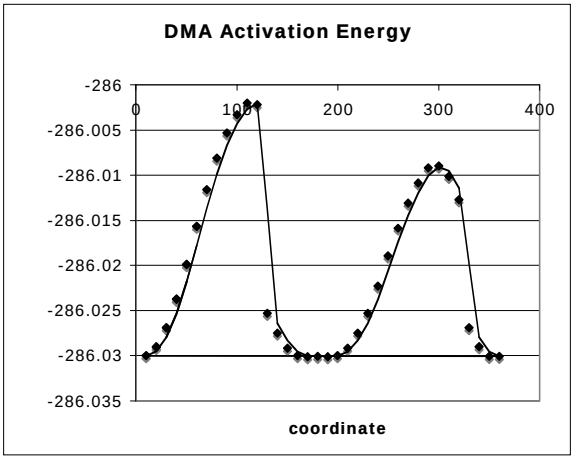
- Draw N,N-dimethylacetamide, formamide, methyl-formamide, or other amide in WebMO. Each group member should do the calculations outlined here for one amide.
- Optimize and examine these structures within two different model chemistries (*ie.* AM1 or HF and 6-31G(d) or others).
- Repeat these optimization calculations (with the same model chemistries as chosen above) in a solvent ($CHCl_3$) instead of the gas phase. Set up the job as you did above. Before submitting the job, go to the Advanced Tab. Select one of the solvents. Then go to the Preview Tab and select "Generate". Change the solvent to "CHCl3". DO NOT select generate again. Submit job.
- Compare the structures (gas versus solvent phases and between amides) and record some pertinent geometrical data (use the JACS pre-lab paper for ideas).
- Carry out a "relaxed" potential energy scan to get at the barrier to isomerization. Do this in the gas phase. 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.

- From the potential energy scan, you will obtain data that looks similar to the following graph:



The activation energy of the reaction can be found from the difference in energy of the valley and the peak. Note that the actual activation energy is the average of the two peaks displayed. The energies associated with the 2nd rotation, the right peak, are lower than the first rotation due to differences in sterics and electronics associated with the molecule.

- Examine the charges on the atoms to gain insight into changes upon isomerization.
- Do a series of calculations on the transition state structure (a 90 degree dihedral). 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***). 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). Record the bond lengths and partial bonds at the transition state. Compare to the 'reactant' and 'product' states.
- Time permitting, complete other calculations that seem pertinent and interesting.

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 literature papers.

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).
3. McQuarrie and Simon, Chapter 28 (on Transition State Theory).