

Analysis of Conformational Influences Within (2*R*,3*R*)-butanediol

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Abstract

(2,3)-Butanediol is a simple polyol with two different isomers: the meso isomer and the racemic isomer. We examined (2*R*, 3*R*)-butanediol in different solvents and investigated its conformational preferences to determine the conformational influences present in (2*R*,3*R*)-butanediol. (2*R*,3*R*)-butanediol serves as a model molecule to understand the conformational influences in more complex compounds such as proteins. Some conformational influences we investigated are steric bulk, intramolecular hydrogen bonding, Coulombic attraction/repulsion, solvent effects, the polarity of the conformer versus polarity of the solvent, and hyperconjugation. This project primarily aimed to understand possible occurrence and effect of hyperconjugation between vicinal hydroxyl (OH) groups, which are present in (2*R*, 3*R*)-butanediol. Hyperconjugation is an interaction between sigma bond electrons and a vicinal, coplanar anti-bonding sigma orbital, which is thought to increase the stability of the system. The methodology employed was ¹H NMR and ¹³C NMR on (2*R*, 3*R*)-butanediol in different solvents. Then we simulated the experimental spectrum on gNMR to extract the coupling constants. We used the Altona equation in order to correlate the coupling constants with dihedral angles, thereby determining the conformation of the compound.

INTRODUCTION

Importance & Application

By investigating the solvent effects within (2*R*, 3*R*)-butanediol we are aiming to discern the conformational preferences within this molecule. We hope to make this molecule a model molecule to help us understand the conformations of larger

molecules such as proteins. Proteins in the body contain numerous amino acids in their peptide chain. These acids fold from the primary structure up to the quaternary structure due to the intramolecular conformational influences among the amino acids:

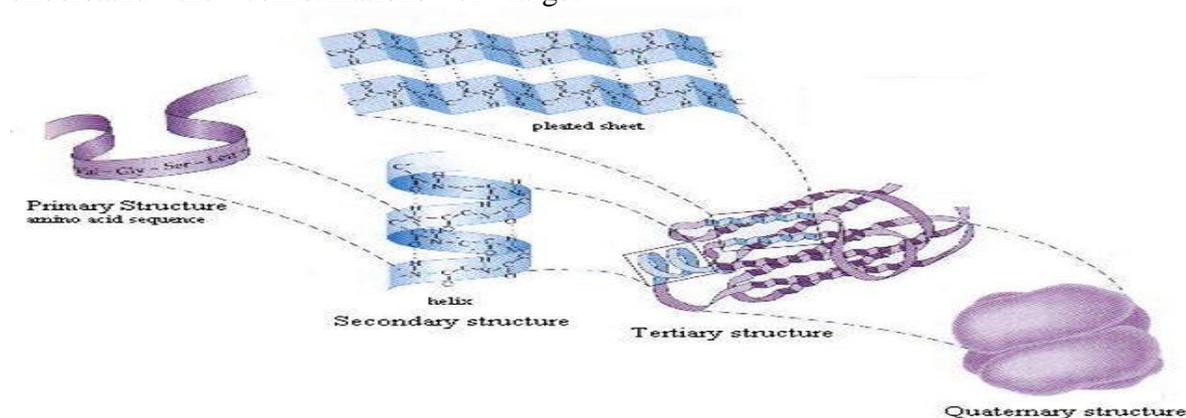


Figure 1: Proteins undergo four different structures, which fold through intramolecular and intermolecular bonding. The hydrogen bonding is a conformational influence that we study.

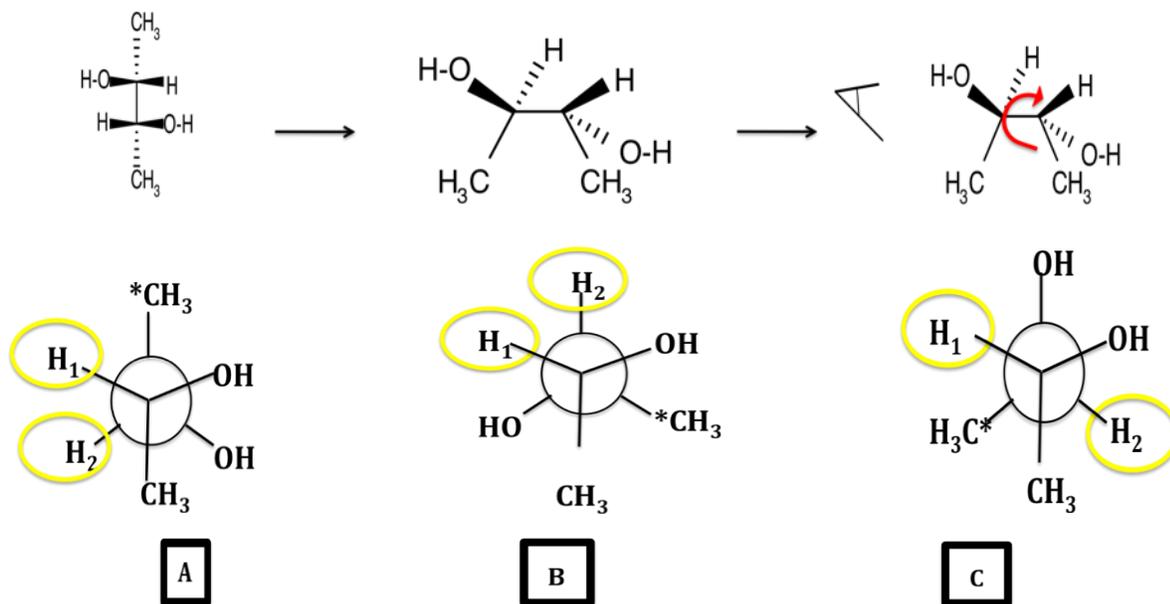


Figure 2: The three conformational isomers of (2R, 3R)-butanediol.

Some conformational preferences outlined in this study are steric bulk, intramolecular hydrogen bonding, Coulombic attraction/

repulsion, solvent effects, the polarity of the conformer versus polarity of the solvent, and hyperconjugation.

Conformational Influences & Predictions

Steric Bulk

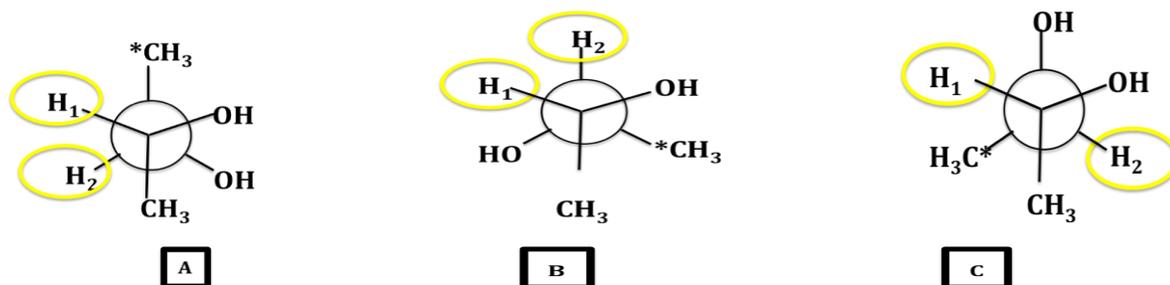


Figure 3: The three conformational isomers of (2R, 3R)-butanediol.

(2R,3R)-butanediol has two types of substituents: the hydroxyl and the methyl groups. The methyl groups will repel each other due to their size. Therefore, since the isomer A has an anti-methyl conformation it is expected to relieve the steric strain of the two methyl groups. Both isomer B and C have the methyl groups in close proximity, and are expected to exhibit more steric strain.

Hydrogen Bonding

All three conformational isomers could possibly exhibit intramolecular hydrogen bonding interactions because they all have vicinal hydroxyl groups. Also, all three isomers may exhibit intermolecular hydrogen bonding with a solvent that allows for this dipole-dipole interaction. Both isomer A and

C have a higher likelihood intramolecular hydrogen bonding because the vicinal hydroxyl groups are gauche.

Coulombic Attraction & Repulsion

The charge attraction or repulsion may occur with the vicinal hydroxyl groups. The hydroxyl groups have the lone pair electrons; therefore, repulsion may occur. Both isomer A and C have the hydroxyl group in close proximity coulombic repulsion between OH groups in A and B would be greater than C. In effect, isomer B has the hydroxyl groups anti to each other; it will be the most stable conformation based purely on the repulsion of OH groups.

Polarity of the Conformer Versus the Polarity of the Solvent

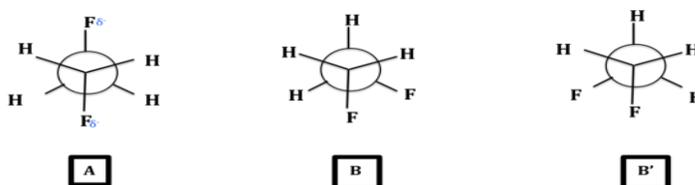


Figure 4: The Three Conformational Isomers of 1,2-Difluoroethane. B and B' are the same

1,2-difluoroethane demonstrates excellent hyperconjugation interactions as illustrated in Figure 5. The electron donation from the σ_{CH} to the σ^*_{CF} illustrates a smooth transition of electrons because the sigma and σ^* bonds are coplanar. Therefore, the donation of electrons has the possibility of occurring. Since the electronegativity of

The polarity of the conformer is due to the diols on rac-2,3-butanediol. This makes the molecule more susceptible to interacting better with very polar solvents such as D_2O versus p-dioxane.

Hyperconjugation

We investigated the presence of hyperconjugation as a means toward the stabilization of a molecule. We will later examine a theoretical study where hyperconjugation was observed, but with (2R,3R)-butanediol we wanted to investigate it at the experimental level. In 2005, Goodman, Gu, and Pophrastic studied the effect of hyperconjugation in 1,2-difluoroethane.

fluorine is the highest, the $C-F \sigma^*$ orbital is a better electron acceptor than the $C-H \sigma^*$ orbital. On the other hand, the $C-H \sigma$ orbital is a better electron donor than the $C-F \sigma$ orbital. A good overlap between the better donor and the better acceptor is only conformation the gauche conformation provides.

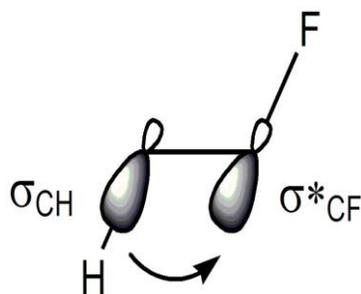


Figure 5: A model illustrating Hyperconjugation in 1,2-difluoroethane

Goodman demonstrated that when C_1-H/C_2-F^* hyperconjugation interactions are removed, the molecule is the most stable when the vicinal F are 180° (the anti conformation). The dark line in Figure 6 shows this. Goodman then demonstrated that 1,2-difluoroethane was at its most stable (F/F

dihedral; 60° and 270° , gauche conformation) when the C_1-H/C_2-F^* hyperconjugation interactions were retained in the theoretical calculation indicated by the dashed line in figure 6. This effect they called the gauche effect.

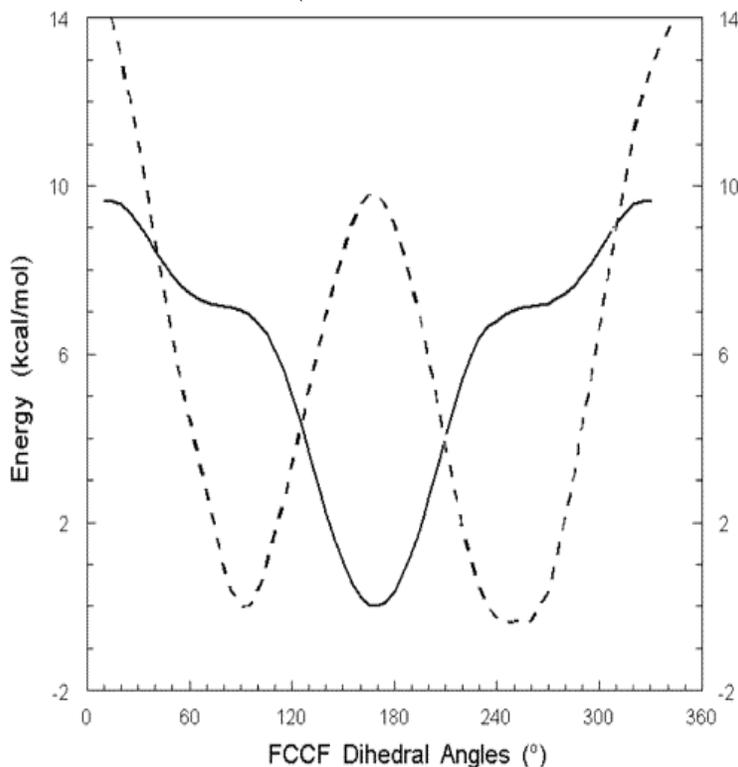


Figure 6: It depicts the fully optimized potential curves obtained: when only the C_1-H/C_2-F^* interactions are removed (—); when only the C_1-H/C_2-F^* interactions are retained with all other interactions expunged (---). Energy zero is arbitrarily taken at minimum of (---) curve.

In racemic-2,3-butanediol, we have two excellent hyperconjugation interactions within isomer A and C as illustrated in Figure. 7 and 9. Hyperconjugation in B is lacking for the

sigma to the anti-sigma electron donation is not coplanar. The expected percentages of A and C is much higher than B.

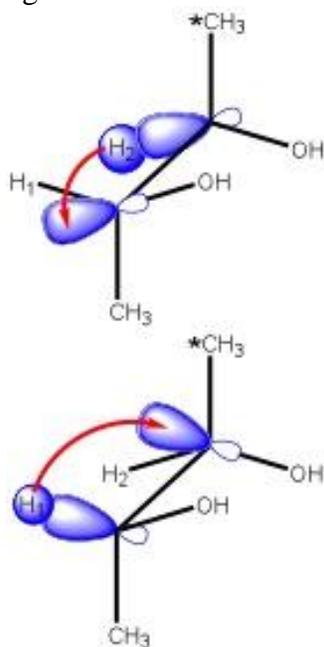


Figure 7: Conformer A

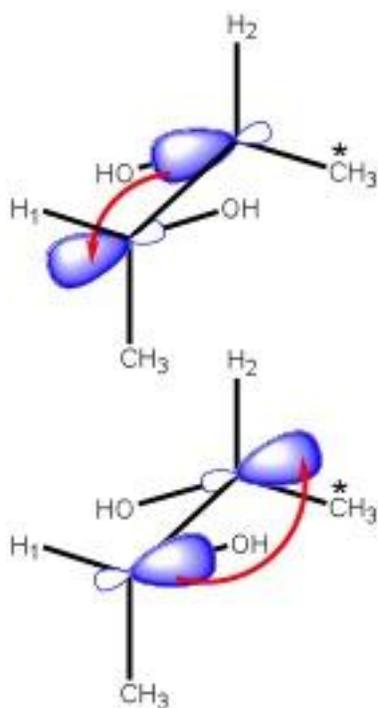


Figure 8: Conformer B

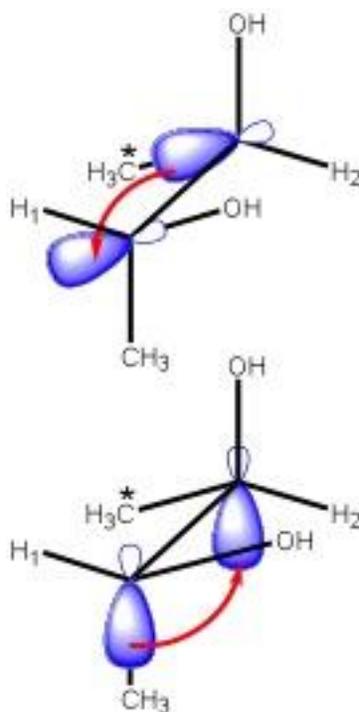


Figure 9: Conformer C

PREVIOUS RESEARCH

1. ^1H NMR Acquired

Previous research students acquired proton NMR to extract the coupling constants from the experimental spectrum. In effect, the

coupling constants acquired would later be used to calculate the percentage of each conformational isomer through the Altona equation.

Table 1: ^1H NMR acquired by previous research students for (2R, 3R)-butanediol

solvent	$J_{5.7}/J_{10.9}$	$J_{5.6}/J_{10.8}$	$J_{5.9}/J_{10.7}$	$J_{6.7}/J_{8.9}$	$J_{6.9}/J_{8.7}$	$J_{7.9}$
D₂O	6.45	not obs.	-0.30	not obs.	not obs.	5.96
methanol-<i>d</i>₄	6.41	not obs.	-0.29	not obs.	not obs.	5.84
ethanol-<i>d</i>₆	6.41	not obs.	-0.32	not obs.	not obs.	5.87
isopropyl alcohol-<i>d</i>₈	6.36	not obs.	-0.31	not obs.	not obs.	6.04
t-butyl alcohol-<i>d</i>₁₀	6.35	not obs.	-0.21	not obs.	not obs.	6.39
DMSO-<i>d</i>₆	6.31	0.01	-0.05	4.73	-0.29	5.52
acetone-<i>d</i>₆	6.41	-0.03	-0.27	4.15	-0.27	6.02
acetonitrile-<i>d</i>₃	7.47	0.01	-0.11	6.27	-0.57	2.39
p-dioxane-<i>d</i>₈	6.15	-0.03	-0.44	4.25	-0.34	5.96

PROBLEMS

2,3-Butanediol has two isomers: the meso and the racemic isomer. The meso isomer's conformational preferences may be calculated using the Altona equation (described in **Problems**) because two of the

three conformations are the same energy. Therefore, we have three unknowns (%A, %B, %B') and three equations relating %A, %B, and %B' (Figure 11). This is illustrated by the Newman projections of B and B' on meso-2,3-butanediol.

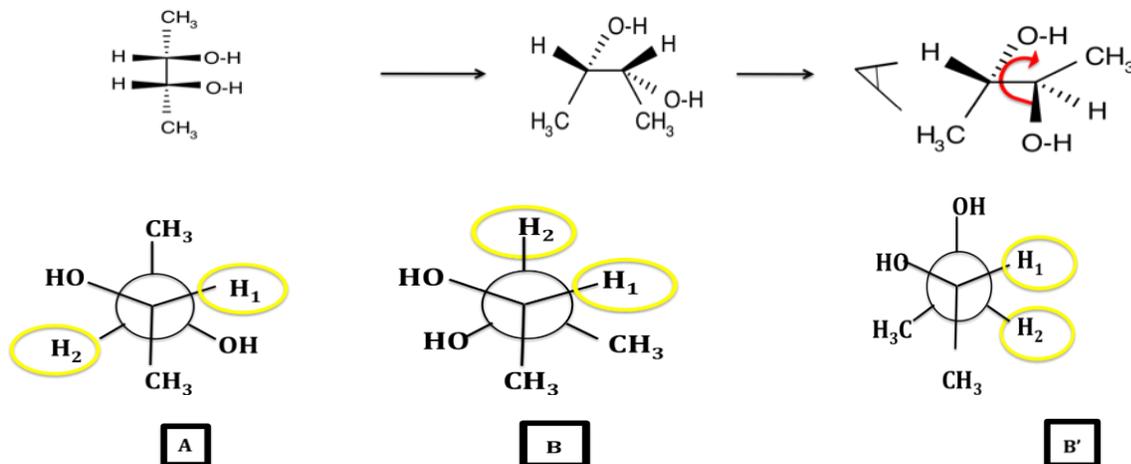


Figure 11: Meso-2,3-butanediol

Unknown: $F_A, F_B, F_{B'}$

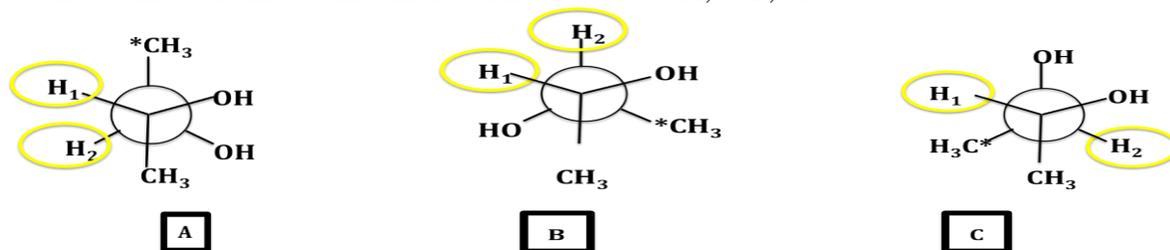
$$J_{12} = (F_A)(J_{12A}) + (F_B)(J_{12B}) + (F_{B'})(J_{12B'})$$

$$F_A + F_B + F_{B'} = 1$$

$$F_B = F_{B'}$$

However, in racemic-2,3-butanediol the situation becomes more complicated because we have three distinct conformers with three

different variables (%A, %B, %C), but only two equations to relate ¹H-¹H J-values with %A, %B, and %C.



Unknown: F_A, F_B, F_C

$$J_{12} = (F_A)(J_{12A}) + (F_B)(J_{12B}) + (F_C)(J_{12C})$$

$$F_A + F_B + F_C = 1$$

$$J_{H_1C_{obs}} = (F_A)(J_{12C}) + (F_B)(J_{12HC}) + (F_C)(J_{12HC})$$

CURRENT RESEARCH

¹³C NMR

We used ¹³C NMR spectroscopy to gather an experimental spectrum. Then, we simulated this experimental spectrum on gNMR to extract the coupling constants. The coupling constants will be used in the Altona equation

to calculate the percentage of each conformer. In effect, we need a J_{C-H} . Therefore, through extensive literature review, we are in search of a method by which to relate ¹³C-¹H coupling constants to dihedral angles.

EXPERIMENTAL DETAILS AND RESULTS

Masses and Volume acquired for deuterated solvents

Table 2: Mass and Volume of Solvent and (2R,3R)-butanediol

Solvent	Mass of (2R, 3R)-butanediol (g)	Volume (mL)
methanol- <i>d</i> ₄	0.0270	0.40
DMSO- <i>d</i> ₆	0.0610	0.40
acetone- <i>d</i> ₆	0.1146	0.40
acetonitrile- <i>d</i> ₃	0.1000	0.40

NMR Acquisition

Table 3: NMR acquisition variations for (2R, 3R)-butanediol

Solvent	Boiling Point (°C)	Temperature (°C)	Number of Scans	# of x-points
methanol- <i>d</i> ₄	64.7	50	8500	64000
DMSO- <i>d</i> ₆	189	50	5000	64000
acetone- <i>d</i> ₆	56.5	50	32000	64000
acetonitrile- <i>d</i> ₃	81.6	50	32000	64000

We varied the temperature (not exceeding the boiling point of the solvent) for the experimental spectrum. In effect, we had to elevate the temperature to receive better resolution of the spectra. We needed excellent resolution in order to see if certain peaks existed or what we observed was just noise from the machine. For the most part, all the solvents used had an elevated temperature of 50°C.

Some solvents needed more scans than others. The solvents that needed less scans tended to

lose their lock signal after a certain time like methanol-*d*₄ and DMSO-*d*₆.

The number of x-points used was consistently 64000. 32000 x-points were utilized initially; however, it was not giving the resolution needed for a proper experimental spectrum.

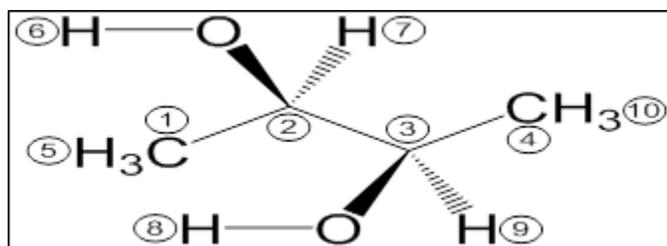
gNMR

We used gNMR to simulate the experimental spectrum. This software calculates the coupling constants of the spectrum.

Some samples underwent “D” and “H” exchange. This exchange occurs when covalently bonded O-H hydrogen exchanges with the deuterium atoms of the solvent.

Therefore, some solvents such as D₂O, methanol, ethanol, isopropyl alcohol, t-butyl alcohol do not have observed “OH” coupling constants.

Table 4: ¹³C NMR coupling constants (Hz) for (2R, 3R)-butanediol



Solvent	chemical shifts (ppm)				
	1/4	2/3	5/10	6/8	7/9
D ₂ O	19.422	73.146	1.129	not obs.	3.610
methanol- <i>d</i> ₄	18.924	72.895	1.112	not obs.	3.511
DMSO- <i>d</i> ₆	18.255	70.510	0.962	4.294	3.379
acetone- <i>d</i> ₆	19.086	72.272	1.073	3.538	3.437
acetonitrile- <i>d</i> ₃	19.898	73.152	1.052	2.859	3.437

Solvent	J_{1-5}/J_{4-10}	J_{1-7}/J_{4-9}	J_{1-9}/J_{4-7}	J_{1-10}/J_{4-5}	J_{1-6}/J_{4-8}	J_{1-8}/J_{4-6}	J_{2-7}/J_{3-9}	J_{2-10}/J_{3-5}
D₂O	126.14	-1.99	1.99	0.28	not obs.	not obs.	142.85	4.49
methanol-<i>d</i>₄	125.6	-1.29	2.35	0.21	not obs.	not obs.	141.02	4.4
DMSO-<i>d</i>₆	125.16	-0.19	1.36	0	not obs.	not obs.	139.84	4.34
acetone-<i>d</i>₆	125.34	-1.24	0.67	0	not obs.	not obs.	140.96	4.47
acetonitrile-<i>d</i>₃	125.71	-0.51	0.35	0	not obs.	not obs.	141.44	4.51

Solvent	J_{2-5}/J_{3-10}	J_{2-6}/J_{3-8}	J_{2-8}/J_{3-6}	J_{2-9}/J_{3-7}	J_{2-10}/J_{3-5}
D₂O	-4.50	not obs.	not obs.	-2.29	4.49
methanol-<i>d</i>₄	-4.40	not obs.	not obs.	-2.02	4.40
DMSO-<i>d</i>₆	-4.34	not obs.	not obs.	-2.37	4.34
acetone-<i>d</i>₆	-4.47	not obs.	not obs.	-2.26	4.47
acetonitrile-<i>d</i>₃	-4.51	not obs.	not obs.	-2.19	4.51

DISCUSSION

Success

About half of the solvents for carbon NMR have been finished. The difficulty lies in finishing the remaining solvents, which do not undergo "D" and "H" exchange because the added OH coupling further complicates the situation.

I finished the ^{13}C NMR experimental and modeled spectra for methanol, acetone, D_2O (gNMR), DMSO, and acetonitrile (experimental).

Failures

In recent experimental trials, the NMR machine needed to be properly tuned for the carbon nuclei. Deuterated ethanol was not locking to the signal. So, I was having huge shimming issues. It would take approximately two hours to shim my

spectrum well enough to obtain a decent spectrum.

In addition, the modeled spectra for deuterated acetonitrile in gNMR had some alignment issues. Therefore, the proton NMR was retaken. However, the new spectrum was giving excellent resolution that the software simulation was having difficulty calculating.

Literature Review

We are looking for a way to correlate the carbon-proton coupling constants to calculate the percentages of each conformational isomer using the Altona equation.

Aydin R., Günther H. pointed out a well-established equation for carbon-proton coupling: Research is conducted to find where this was established and how the coupling constants are applied.

$${}^nJ(^{13}\text{C}, ^1\text{H}) = (y_{\text{H}}/y_{\text{D}}) J(^{13}\text{C}, ^2\text{H}) / 6.5144^n J(^{13}\text{C}, ^2\text{H})$$

FUTURE RESEARCH

I will continue to collect data on the remaining solvents which are p-dioxane,

ethanol, t-butyl alcohol, isopropyl alcohol, and the gNMR for acetonitrile. Also, I will continue to search for a method that relates ^{13}C - ^1H coupling constants to dihedral angles.

References

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