

Quantum Mechanical Energy Minimization and Solvation Energies for GABA

Abstract

GABA is an inhibitory neurotransmitter that naturally suppresses neuron action potentials by interacting with positive and negative ion channel gradients. This results in altered membrane potentials, and thus solvent effects. We studied these solvent effects as well as conformational energy minimizations using the quantum mechanical program GAMESS. Specifically, we attempted to determine the solvation energies of four possible conformers in DMSO and water. We also attempted to determine the minimal energy values of these same conformers using Hartree-Fock energy calculations. Some of our calculations converged at reasonable energy values; however, we selected several errant input parameters and coordinates, we also should have used an alternative program for geometry minimization.

Introduction

Gamma aminobutyric acid (GABA) is a naturally occurring amino acid that behaves as an inhibitory neurotransmitter¹. It is a highly studied molecule due to its potential practical applications as a naturally occurring sleep aid and anti anxiety supplement². GABA and its receptors, GABA-A and GABA-B, are typically implicated with a change in cellular membrane potential³. For this reason, we hypothesized that a quantum mechanical study of the electrostatic interactions between GABA and a solvent would prove scientifically relevant. In particular, we are interested in GABA's interactions with water and DMSO. We chose water because of its obvious relevance to biological systems and we chose DMSO because it is frequently used during analytical experiments. In order to perform this experiment we used the program GAMESS and specifically designed input files for our molecule. We chose to use GAMESS because it has user friendly input parameters and is known to effectively model solvation energies. Within GAMESS the most important parameter for this experiment was the Polarizable Continuum Model (PCM). In PCM solvent molecules are not recognized individually, for the sake of calculation difficulty, but instead as a polarizable continuum⁴. In this continuum all of the molecules are assigned a uniform dielectric constant value⁴.

We also performed an experiment earlier in the quarter where we ran a conformational search for GABA using molecular mechanics methods, specifically the program BOSS. These conformational searches used Newtonian motion calculations rather than more accurate quantum mechanical calculations⁴. We will compare the energies from the conformational search with the quantum mechanically calculated Hartree-Fock energies from GAMESS. The Hartree-Fock based energies are calculated with respect to the nuclei-nuclei and nuclei-electron interactions using the Schrodinger equation. The dynamic electron-electron interactions are typically only approximated by ignoring excitations within empty orbitals⁵. It is important to note that the input conformations for the GAMESS calculations were the outputs for the conformational

search, so we expect that the GAMESS analysis will result in more accurate energy values. This should remain true, despite the fact that we utilized Hartree-Fock based energy calculations. That being said, it would not be surprising if the lack of dynamic electron-electron interactions resulted in energy values that were higher than expected values. We used a coupled cluster double basis set which builds multi-electron wavefunctions to somewhat account for electron-electron correlations⁶. This is a relatively rudimentary correction for the ab initio Hartree-Fock calculation described above.

Methods

Input File Parameters:

Quantum Mechanical Energy Minimization:

The quantum mechanical energy minimization files contained GAMESS keywords for: conformational minimization, atomic Z-matrix coordinates, 3N-6 internal coordinates, a ccd basis set, the number of functions to represent the molecular orbitals, and geometry based characteristics for each conformer. Specifically, we denoted 42 geometric variables, spherical harmonic basis, 6 gaussian functions, 1 heavy atom polarization function, and 1 light atom polarization function.

Quantum Mechanical Solvation Energy:

The quantum mechanical energy minimization files contained keywords denoting: a restricted Hartree-Fock self consistent field wavefunction, the same Z-matrix coordinates defined in the energy minimization, the 3N-6 internal coordinated, spherical harmonic basis, standard DMSO and H₂O Polarizable Continuum Model specifications, ccd basis sets, Huckel initial orbitals, a gradient convergence tolerance, and geometry characteristics of each conformer.

Initial Conformations for Both Calculations:

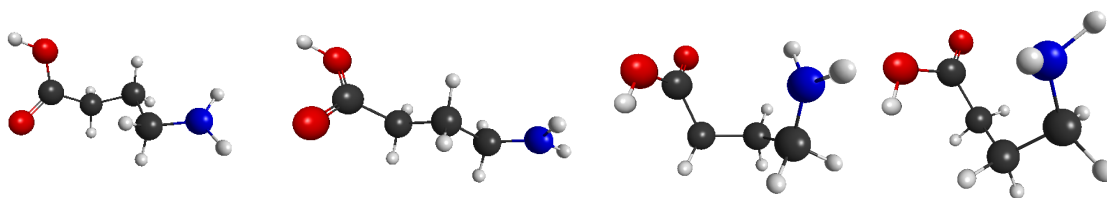


Figure 1: Initial GABA Conformations

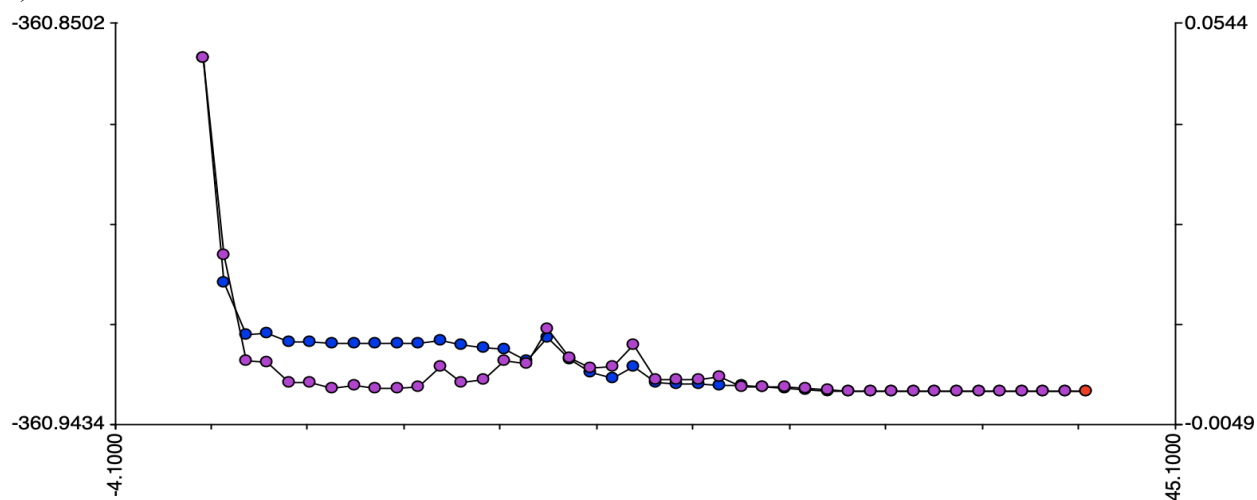
This figure shows the four initial structures of GABA used in both calculations.

Results

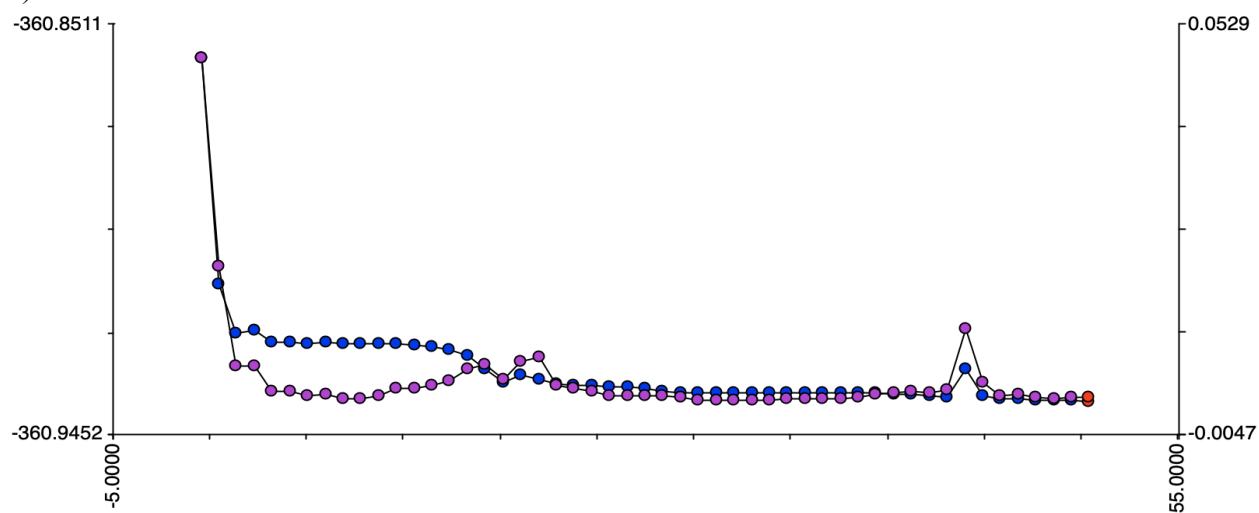
After running four energy minimization input files, four H₂O solvation energy input files, and four DMSO solvation energy input files we obtained the following solvation energies and minimization energies. Not all of these calculations proceeded as planned; however, this will be discussed below. Relevant convergence diagrams are also shown below.

Energy Minimization Convergence Graphs:

a)



b)



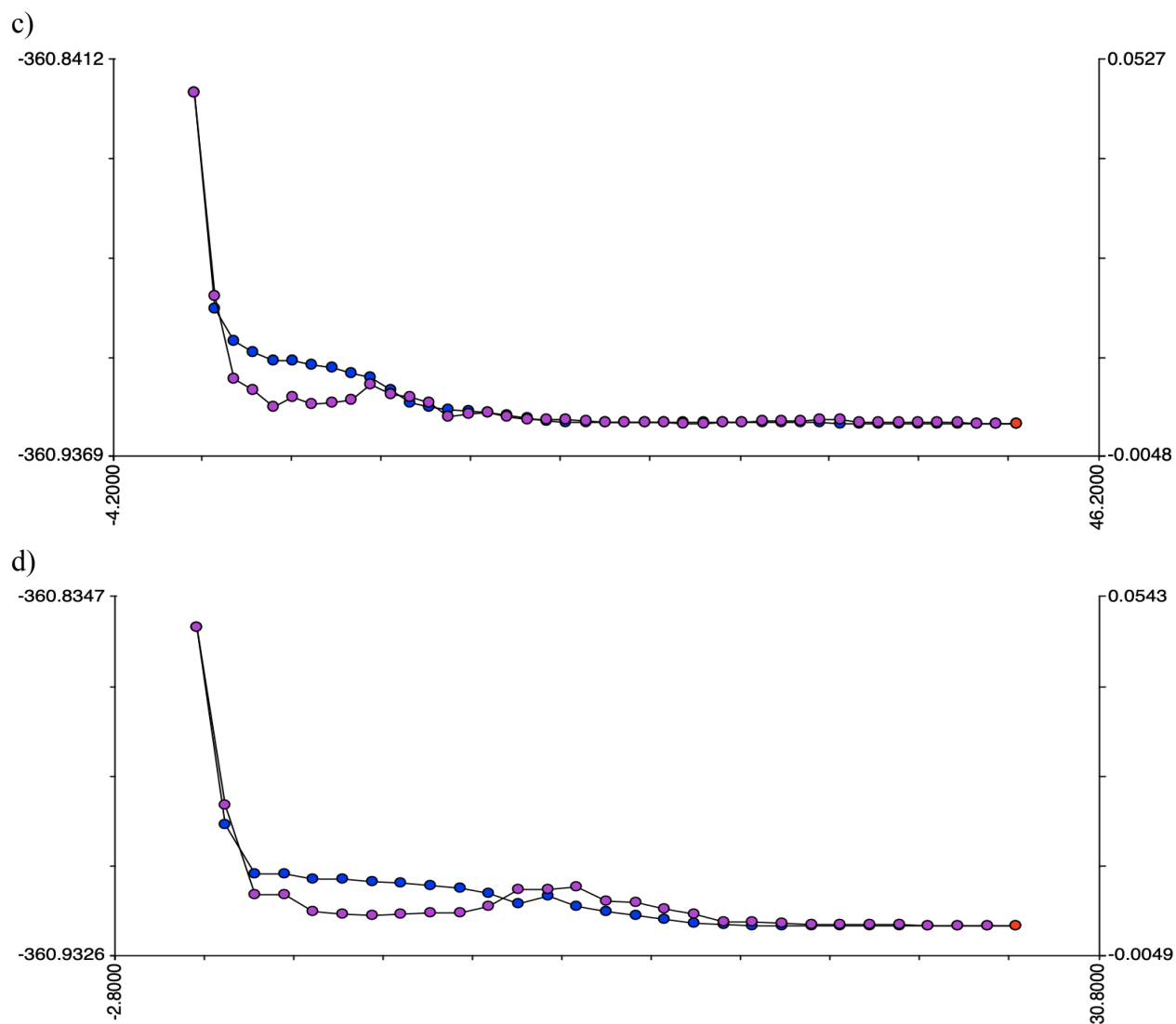
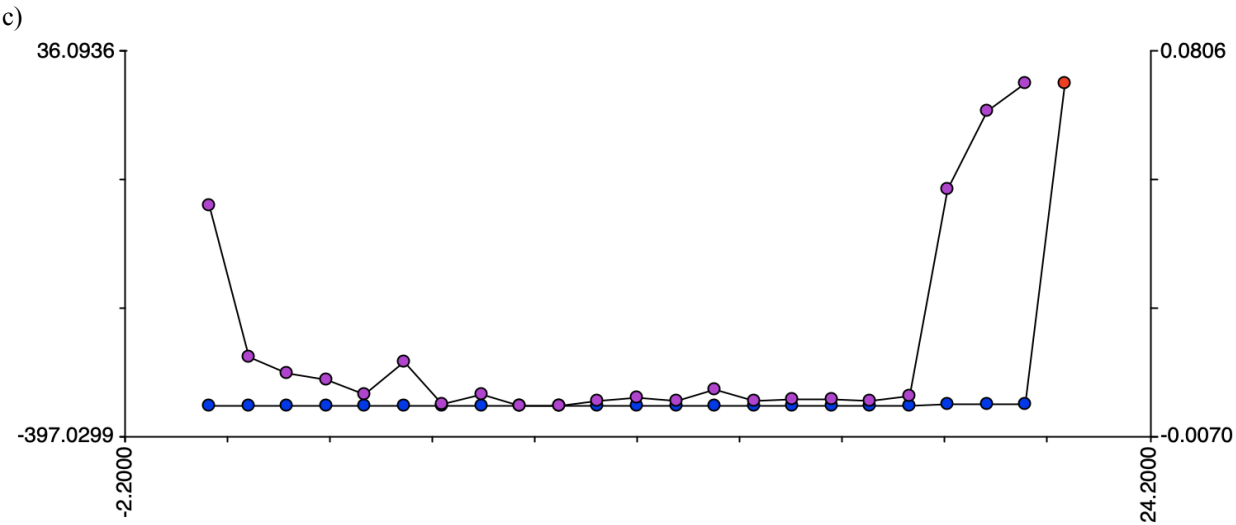
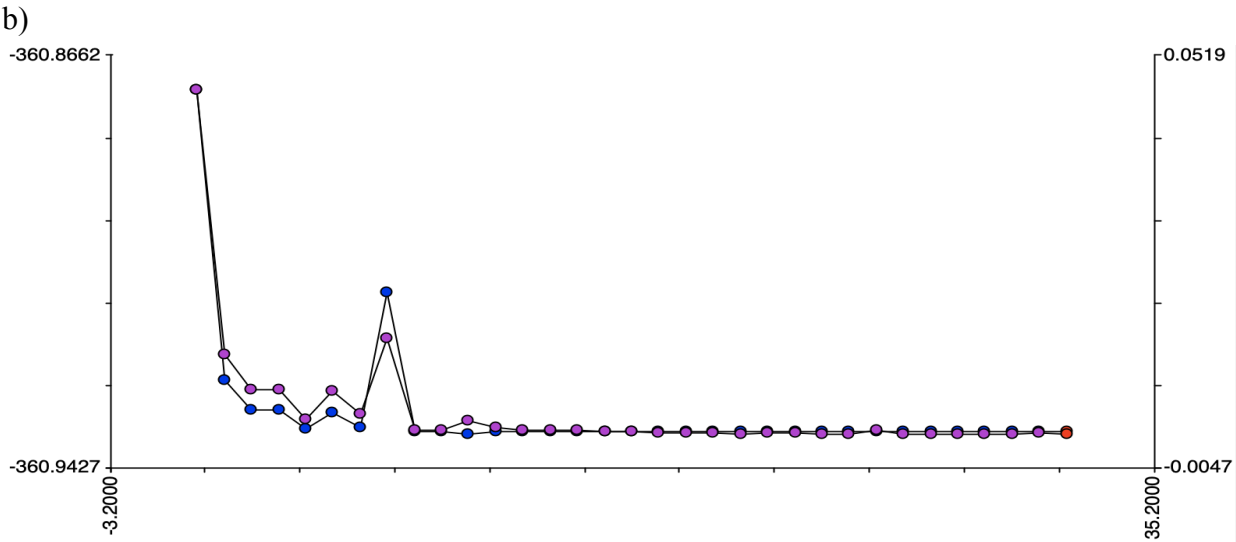
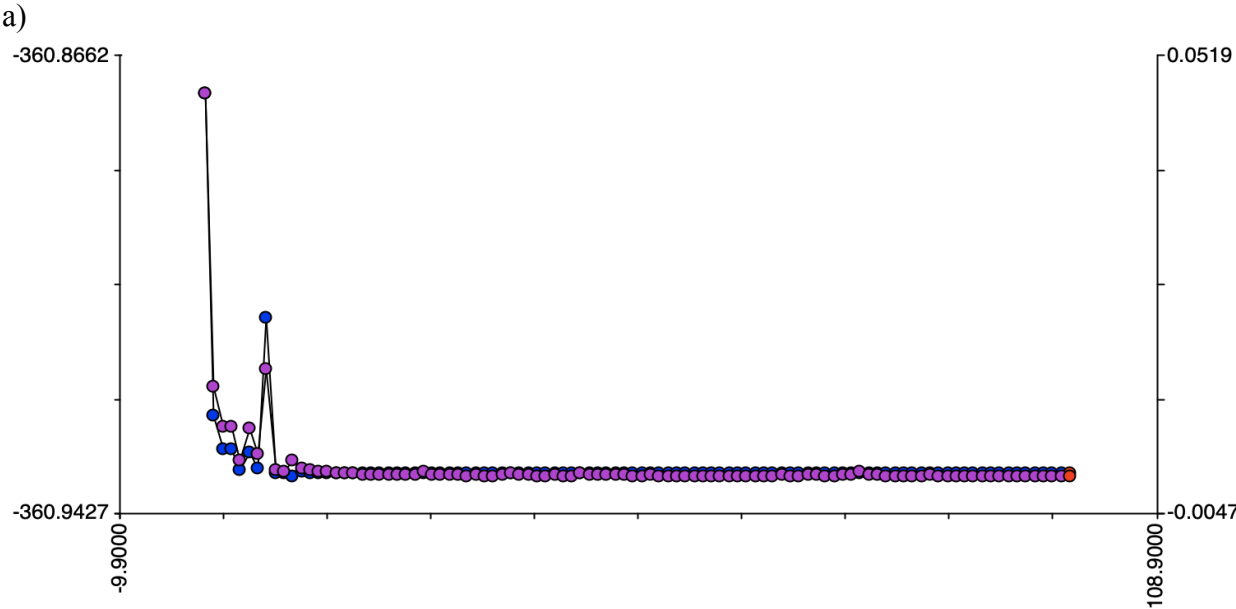
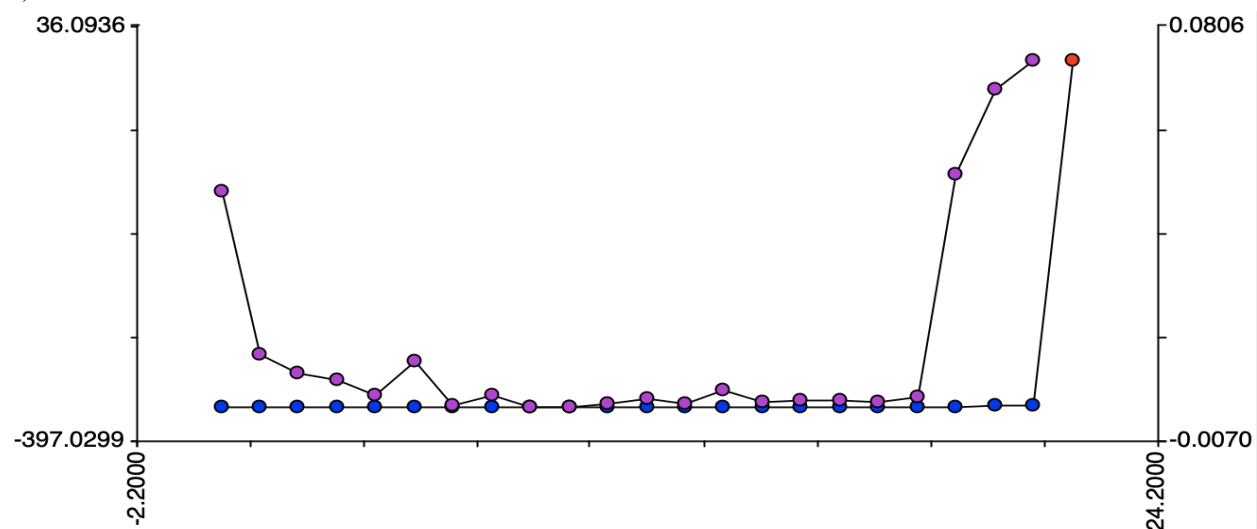


Figure 2: Energy Convergence Graphs for Energy Minimization

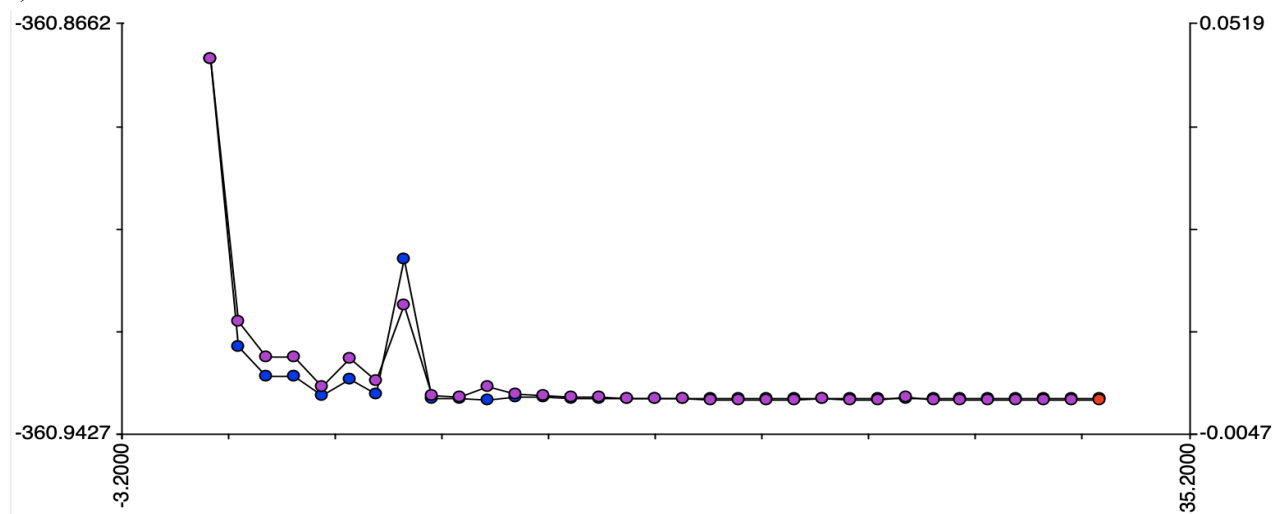
These four graphs show the convergence of the four conformations of GABA with the x-axis representing the number of steps and the y axis representing the energy in A.U. on the left and RMS gradient on the right. a) This graph corresponds to conformer 1 and converges in 52 steps. b) This graph corresponds to conformer 5 and does not converge. c) This graph corresponds to conformer 13 and converges in 43 steps. d) This graph corresponds to conformer 17 and converges in 29 steps.



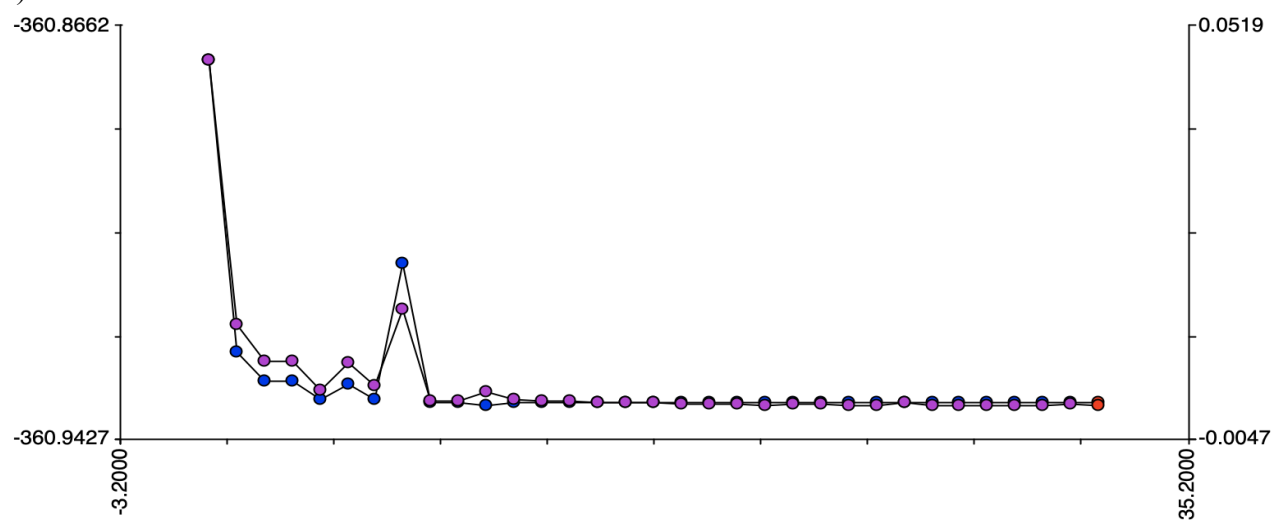
d)



e)



f)



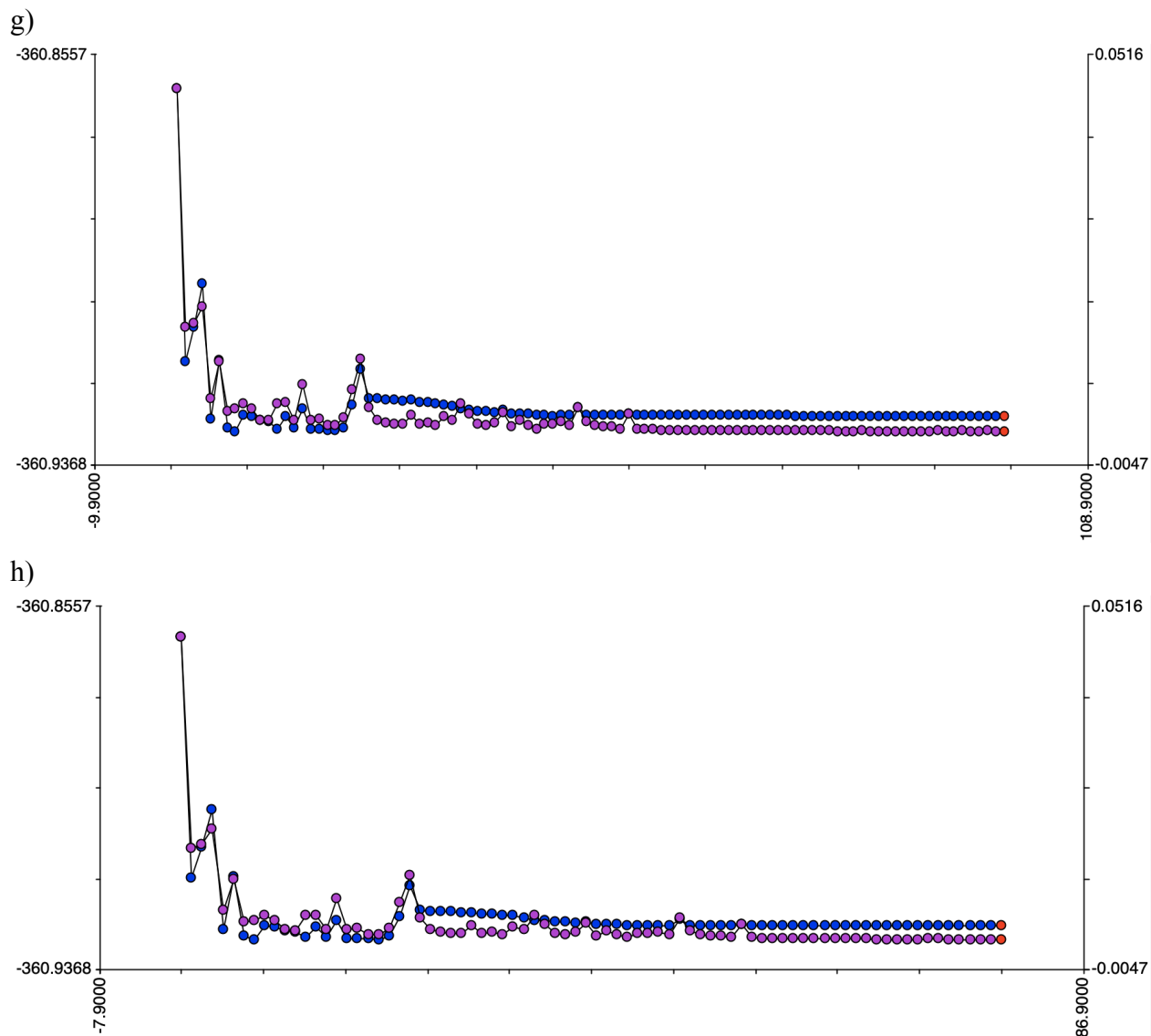


Figure 3: Energy Convergence Graphs for Total Solvation Energies

These eight graphs show the convergence of the four conformations of GABA in DMSO and H₂O. The x-axis represents the number of steps and the y axis represents the energy in A.U. on the left and RMS gradient on the right. a) This graph corresponds to conformer 1 in DMSO and converges in 100 steps. b) This graph corresponds to conformer 1 in H₂O and converges in 33 steps. c) This graph corresponds to conformer 5 in DMSO and does not converge. d) This graph corresponds to conformer 5 in H₂O and does not converge. e) This graph corresponds to conformer 13 in DMSO and converges in 33 steps. f) This graph corresponds to conformer 13 in H₂O and converges in 33 steps. g) This graph corresponds to conformer 17 and does not converge. h) This graph corresponds to conformer 17 and does not converge.

	Energy Minimization (A.U.)	Total Free Energy in Water (A.U.)	Total Free Energy in DMSO (A.U.)
Conformation 1	-360.9356176	-360.9358939	-360.9359101
Conformation 5	-360.9373682	N/A	N/A
Conformation 13	-360.9288916	-360.9358939	-360.9358939
Conformation 17	-360.9244130	-360.9269505	-360.9269521

Figure 4: Minimization and Solvation Energies for GABA

This figure provides energy minimization values and total free energies of solvation in atomic energy units for the four conformers of GABA.

Discussion

Conformational Energy Minimization:

Overall, our conformational minimizations were successful for conformers 1, 13, and 17. They all converged although not particularly efficiently. The same can not be said for conformer 5, which never fully converged and the output file failed halfway through the calculation. The inefficiency and the failure of conformer 5 can be explained by both our choice of GAMESS as the quantum calculation program and by our choice of z-matrix valence coordinates. Valence coordinates are redundant; meaning that there are more coordinates than are required by the standard $3N-6$ evaluation⁷. Strong linear and nonlinear coupling is created between coordinates after arbitrarily omitting some of these extra valence coordinates⁷. Essentially, the Z-matrix method is an inefficient method to store atomic coordinates in larger molecules. This is particularly damaging for geometry optimizations, where calculations scale based on the number of atoms. A solution to this problem would have been to use natural coordinates⁷. Proper natural coordinates converge much faster in the initial steps. For our molecule, natural coordinates would consist of bond stretching coordinates, redundancy free linear combinations of bond angles and torsions in what are called deformational coordinates⁷. Aside from this, we would have been better off using a program better suited for first and second order methods for geometry optimizations, such as Dalton. The main cause of failure for conformation 5 is unknown; however, after analyzing the output file, it seems possible that there were simply not enough steps. Our professor created a more optimal input file for this conformation and got it down to 18 steps. If time had permitted, we would have rerun the calculation using the last iteration of the failed attempt. If this still proved to be insufficient, we would have redesigned the input file to contain natural coordinates and run the calculation in Dalton. To improve the accuracy of our data, we would have run all of these calculations using an improved ab initio post Hartree-Fock method, perhaps MP2 or MP3. One of these would have more accurately determined the energies because they add electron correlation effects. Our results are fairly consistent with literature results also featuring four relatively similar energy conformers⁸.

Total Solvation Energies:

Our total solvation energies were successfully determined for conformers 1 and 13, but did not converge for conformers 5 and 17. Conformer 5 continued to exhibit strange behavior. In figure 3c-d, the energy appears to start to converge before rapidly increasing for an unknown reason. To solve this problem, we would once again convert the z-matrix internal coordinates to natural coordinates in order to decrease the difficulty of the calculations as well as correct whatever error this particular conformation is exhibiting. I would not switch to Dalton, although Dalton is also capable of calculating solvation energies, because GAMESS is very effective at this particular calculation. It would be interesting to attempt an Effective Fragment Potential Method, so that we could compare the two methods with our molecule. EFP takes into account not just polarizability, but also electrostatics, dispersion, and exchange-repulsion interactions for more accurate solvation energy calculations⁹. Furthermore, if time had permitted we also would have tested more solvents. Both of our solvents are highly relevant, but neither are nonpolar. Conformer 17, seen in figure 3g-h, also behaved quite strangely where both energy calculations leveled off, but did not approach the same value. It is difficult to say how this calculation went wrong seeing as the input files were nearly identical to the other three, aside from the values of the internal coordinates of course. For this reason, we would once again alter our optimization coordinates. Our energy values are fairly arbitrary because we could not find supporting or opposing literature. We can still compare the relative energies though. Doing so shows that conformation 1 in H₂O is the lowest in energy and thus the most stable and that conformation 17 in water was the highest in energy. Do note that this value did not properly converge and is likely erroneous.

Conclusion

We have successfully quantum mechanically modeled the conformationally minimized energy of GABA using GAMESS. We also successfully modeled solvation energies using the Polarizable Continuum Model on GAMESS. We encountered program errors and we poorly chose a handful of input parameters in both experiments. Overall we have obtained data that can be improved upon, in part due to our limited experience and time constraints, but they still provide us with insight into the energetics of the molecule.

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