# Exploring the Conformational Landscape of Amino Acids in Solid Parahydrogen Matrices through *Ab Initio* Calculations

by

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B.Sc., University of Alberta, 2018

# A THESIS SUBMITTED IN PARTIAL FULFULLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

### **Master of Science**

in

## THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Chemistry)

The University of British Columbia

(Vancouver)

April 2021

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Exploring the Conformational Landscape of Amino Acids in Solid Parahydrogen Matrices through Ab Initio Calculations

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#### Abstract

It is well known that amino acids are the building blocks for proteins, and as such, likely played a critical role in the origin of biological life. When in the solid phase, or in solution, amino acids take on a zwitterionic form, enabling a plethora of stabilizing intermolecular interactions. However, prior to understanding amino acids in the bulk phase, one must first characterize them in their neutral form. Due to the conformational flexibly and thermal instability of amino acids, this is best accomplished through the use of high-resolution matrix isolation Fourier transform spectroscopy in conjunction with high level *ab initio* calculations. The vibrational spectrum of  $\alpha$ serine is reported for the first time within a solid parahydrogen matrix, in which ten conformers were identified, thereby supporting the claim that solid parahydrogen matrices are superior to other noble gas matrices for the analysis of highly flexible molecules. Assignment of the vibrational transitions was accomplished through the use of quantum chemical calculations at both the DFT and MP2 levels of theory. Additionally, preliminary TD-DFT calculations indicate that the first singlet excited state of  $\alpha$ -alanine is a dissociative state, in which, upon excitation  $\alpha$ -alanine forms hydrocarboxyl (HOCO) and ethylamine radicals through a Norrish type I pathway. the Interestingly, it is predicted that both the first and second singlet excited states are dissociative states for  $\alpha$ -alanine conformers displaying strong hydrogen bonds between the carboxyl hydrogen and amine lone pair, indicating that noncovalent interactions play a substantial role in both the ground and excited state potential energy surfaces of amino acids.

### Lay Summary

Prior to understanding the role of amino acids in complex biological systems, one must first understand how they behave in isolated environments. The vibrational frequencies of these molecules enable one to assess the strength of bonds within the molecule. Thereby allowing for one to experimentally identify the physicochemical properties of the molecule. In this thesis the conformational landscape of gaseous  $\alpha$ -serine trapped in solid parahydrogen matrices is investigated through the use of Fourier transform infrared spectroscopy (FTIR) and quantum chemical calculations. In addition, the excited states of neutral  $\alpha$ -alanine are briefly discussed through the context of quantum chemical calculations.

## Preface

All of the work presented in this thesis was completed under the supervision of Dr. Takamasa Momose in the Chemistry Department at the University of British Columbia, Vancouver campus.

Experimental spectra of  $\alpha$ -serine presented within this thesis were collected by Shin Toh and Alethea Lee during the summer of 2016. I was responsible for the analysis of said experimental data, including all relevant quantum chemical calculations. Additionally, all of the calculations presented for  $\alpha$ -alanine were performed by me.

All *ab initio* calculations presented herein were completed on Computed Canada clusters.

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# Glossary

AM1	Semiempirical Austin Model 1 Method	
aug-cc-pVTZ	Dunning's Correlation Consistent Augmented Triple Zeta Basis Set with Additional Polarization and Diffuse Functions.	
BJ	Becke-Johnson Damping	
B3LYP	Becke's 3-Parameter Lee-Yang-Parr Hybrid Functional	
B3LYP-D3BJ	B3LYP Functional with D3 and BJ Empirical Corrections	
CBS	Complete Basis Set	
CI	Configuration Interaction	
CIS	Configuration Interaction Singles	
CIS(D)	Configuration Interaction Singles and Perturbative Doubles	
CC	Coupled Cluster Theory	
ccm	Cubic Centimetre per Minute	
cc-pVTZ	Dunning's Correlation Consistent Augmented Triple Zeta Basis Set with Additional Polarization Functions.	
cc-pVTZ-F12	Correlation Consistent Triple Zeta Auxiliary Basis Set with Additional Polarization Functions for Explicitly Correlated Calculations	
cc-pVQZ/C	Correlation Consistent Quadrupole Zeta Auxiliary Basis Set for the Resolution of Identity Approximation	
CCSD	Coupled Cluster Singles and Doubles	
CCSD(T)	Coupled Cluster Singles, Doubles, and Perturbative Triples	
CCSD(T)-F12	Explicitly Correlated Coupled Cluster Singles, Doubles, and Perturbative Triples	
DC	Direct Current	
def2-TZVPD	Alhrichs Split-Valence Triple Zeta Property Optimized Basis Set with Additional Polarization and Diffuse Functions	
DFT	Density Functional Theory	
DVPT2	Depurturbed Second Order Vibrational Perturbation Theory	
D3	Grimme's Empirical Atom-Pairwise Dispersion Correction	
EOM	Equation of Motion	
FCI	Full Configuration Interaction Theory	
FPA	Focal Point Analysis	

FTIR	Fourier Transform Infrared
FWHM	Full Width Half Max
HB	Hydrogen Bond
HF	Hartree-Fock
IR	Infrared
MCT	Mercury Cadmium Telluride
MI	Matrix Isolation
MI-FTIR	Matrix Isolation Fourier Transform Infrared
MIR	Mid-Infrared
MPn	$n^{\text{th}}$ Order Møller-Plesset Perturbation Theory
MP2	Second Order Møller-Plesset Perturbation Theory
MW	Microwave
NCI	Noncovalent Interactions
NIR	Near-Infrared
NTC	Negative Temperature Coefficient
PED	Potential Energy Distribution
PES	Potential Energy Surface
QTAIM	Quantum Theory of Atoms in Molecules
RI	Resolution of Identity
SPT	Simple Perturbation Theory
UV	Ultra-Violet
VPT2	Second Order Vibrational Perturbation Theory
VEDA	Vibrational Energy Distribution Analysis
ZPE	Zero-Point Vibrational Energy

### Acknowledgments

I would like to express my appreciation to my research supervisor, Dr. Takamasa Momose, for his guidance and support throughout my studies. In addition, I would like to express my appreciation to Dr. Manish Vashishta, who taught me a number of different laboratory skills, and provided a helpful hand whenever needed. I would also like to thank current and previous lab mates for their fruitful discussions and banter, including, in no particular order, Dr. Eric Miller, Jiahong Hu, Hatsuki Otani, and Brendan Moore. Finally, I offer my sincere gratitude to my family and girlfriend, Julia Lu, for their extended and unconditional support throughout my studies.

#### **1. Introduction**

#### 1.1. Amino Acids and Molecular Spectroscopy

Organic compounds containing an amino and carboxyl functional group are typically referred to as amino acids, and they are an essential component to biological life. In fact, it has been hypothesized that amino acids were deeply involved in the prebiotic processes responsible for triggering the origin of life.<sup>1</sup> As a result of their biological importance, amino acids have been the subject of countless investigations spanning every scientific discipline. In total there are over 500 naturally occurring amino acids, however, only 20 of these appear in the genetic code of biological species.<sup>2</sup> When amino acids are dissolved in solution or in the solid phase, they take on a zwitterionic form enabling stabilizing intermolecular interactions with the surrounding molecules. Unlike in the solid phase, amino acids in the gas phase are chemically neutral and stabilize themselves via the intramolecular interaction of partial charges. These stabilizing intramolecular interactions include hyperconjugation and hydrogen bonding, however, the presence of destabilizing steric crowding is also possible. Prior to understanding the complex behaviors of molecules in biological settings, one must first completely understand said molecules in an environment free of external perturbation. However, as a result of the thermal instability and low vapour pressure of amino acids,<sup>3</sup> investigations into their neutral form are rather scarce, and as such, the conformational landscape of neutral amino acids remains largely unknown.

In addition to providing crucial information regarding the physicochemical properties of amino acids, investigations into their neutral form enables the identification of amino acids in interstellar space.<sup>4</sup> Identification of amino acids in interstellar space became a hot topic upon the identification of amino acids, diamino acids, nucleobases, and hydrocarbons on the Murchison meteorite, which is a carbonaceous chondrite meteorite, in 1969.<sup>1</sup> The search for amino acids in interstellar space led to questions regarding the stability of amino acids in the presence of ultraviolet (UV) irradiation. Studies into the photostability of amino acids indicate that amino acids may undergo racemization, <sup>5</sup> conformational isomerism,<sup>6</sup> or degradation upon UV irradiation.<sup>7</sup> The latter is of particular interest as it indicates that amino acids may be indirectly detected in interstellar space through the detection of the photoproducts. However, just as was the case with the conformational landscape, the photoproducts from neutral amino acids are largely unknown as a result of experimental and computational complexities.

One popular technique for probing the conformational landscape of molecules is matrix isolation (MI) spectroscopy.<sup>8</sup> Just as the name implies, MI spectroscopy involves the trapping of a target species in an inert matrix kept at cryogenic temperatures, in which the matrix is typically composed of an inert gas such as argon, neon, nitrogen, xenon, or krypton, but in the case of this thesis, solid parahydrogen is utilized. Unlike other gas phase experiments, the MI technique enables one to probe not only the ground state, but also the excited state dynamics of molecules via *in-situ* irradiation of said trapped molecules. However, coupling the use of MI spectroscopy with *ab initio* calculations enables one to accurately investigate both, the ground and excited states.

The work presented in this thesis aims to extend the previous investigations into the physicochemical properties of  $\alpha$ -serine through the use of solid parahydrogen MI-FTIR spectroscopy and high-level *ab initio* calculations. In which the noncovalent intramolecular interactions present in the conformers of  $\alpha$ -serine will be used to aid in their experimental identification. Variation of the sublimation temperature was utilized to further aid in the experimental assignment. This work represents the first study to consider all known low energy  $\alpha$ -serine conformers during the assignment process. Additionally, preliminary results for the investigation into the excited states of  $\alpha$ -alanine are briefly introduced.



Figure 1.1 Skeletal formulas for the L- and D-enantiomers of  $\alpha$ -serine (top) and  $\alpha$ -alanine (bottom). L-enantiomer is on the left for both molecules, and  $\alpha$  denotes the chiral carbon.

#### **1.1.1.** Introduction to $\alpha$ -serine

 $\alpha$ -serine, with a molecular weight of 105.09 g mol<sup>-1</sup> is one of the smallest biologically relevant amino acids being only larger than glycine and alanine. As seen in Figure 1.1, five torsions in  $\alpha$ -serine exist where, upon the internal rotational about said torsion, a new conformer is formed. In

order for a given molecular configuration to be a conformer, the configuration must be located at a local minima on the ground state potential energy surface. The internal rotations of interest are summarized below in Table 1.1, along with an additional skeletal formula of  $\alpha$ -serine which serves as a pictorial representation of said torsions. Of the five torsions of interest, there are two 3-fold internal rotations, two 2-fold, and one 6-fold internal rotation, yielding 324 potential configurations of  $\alpha$ -serine. Unfortunately, as a result of the substantial number of intramolecular interactions present in  $\alpha$ -serine, those 324 configurations do not accurately represent the full ensemble of possible conformers. Due to the large number of possible conformers, many theoretical studies did not consider the full set of trial structures, and as result of this, often missed key low energy conformers throughout their analyses.<sup>9,10,11,12,13,14,15</sup>

λ	Torsion	<b>Considered Angles</b>	Figure
$\lambda_1$	C - C(0) - 0 - H	0, 180	0
$\lambda_2$	N - C - C(0) - O(H)	-150, -90, -30, 30, 90, 150	
$\lambda_3$	C - C - N - H	-60, 60, 180	
$\lambda_4$	N - C - C - O(H)	-120, 0, 120	
$\lambda_5$	$C - C(H_2) - 0 - H$	-120, 0, 120	NH <sub>2</sub>

Table 1.1 Summary of the torsion considered by Gronert and O'Hair for  $\alpha$ -serine.

In 1995, Gronert and O'Hair published the first large-scale study on  $\alpha$ -serine.<sup>16</sup> They sampled the 324 trial structures mentioned above and shown in Table 1.1, with the semiempirical AM1 method identifying 73 unique configurations, which, upon refinement at the HF/6-31G\* level of theory, was reduced to 51 unique conformations. All of the reported conformers were within 50 kJ mol<sup>-1</sup>. It is worth mentioning that HF/3-21G\* was first used to refine the AM1 structures, reducing the number of stable configurations from 73 to 54. Additional refinement with HF/6-31G\* further reduced the number of configurations from 54 to the final value of 51. As a result of the incomplete ensemble of conformers initially considered, a number of low energy conformers were missed. Unfortunately, a number of experimental studies used this publication as a theoretical basis, and as such, they did not consider all possible low energy conformations, which will be discussed below.

In 2005, Miao *et al.* employed B3LYP/6-31G\* to screen Gronert and O'Hair's 324 structures, yielding 83 unique configurations, which upon further refinement with B3LYP/6-311+G\*\* reduced that number to 74.<sup>17</sup> Interestingly, increasing the level of theory to B3LYP

resulted in the discovery of an additional 23 stable configurations, which is the first indication of the importance of electron correlation in  $\alpha$ -serine. Despite having explicitly mentioned the importance of including the full ensemble of possible conformers, this study suffered the same fate as that of Gronert and O'Hair. That is, they missed a number of key low energy conformers as a result of using an incomplete set of trial structures.

In 2016, He and Allen sampled 15,552 configurations of  $\alpha$ -serine at the HF/6-31G\* level of theory, identifying 89 unique configurations.<sup>18</sup> Hence, consideration of the full ensemble obtained an additional 38 unique configurations. Further refinement with MP2/cc-pVTZ reduced the number of stable configurations to 85. In short, the 15,552 starting configurations were constructed from the simultaneous variation of six large-amplitude modes, which are listed below in Table 1.2. Upon optimization with MP2, 12 configurations were identified to be within 12 kJ mol<sup>-1</sup>, and their relative energies were calculated with the highly accurate Focal Point Analysis (FPA). At the time this thesis is being written, He and Allen have presented the most comprehensive computational analysis on the ground state configurations of  $\alpha$ -serine. It is worth mentioning that a quick comparison of Table 1.1 and Table 1.2 show that Gronert and O'Hair failed to account for the inversion of NH<sub>2</sub>, in addition to not considering many possible configurations resulting from rotation about the C – N and C<sub>4</sub> – C<sub>6</sub> torsions.

τ	Mode	Rotation	Figure <sup>a</sup>
$ au_1$	NH <sub>2</sub> inversion	2-fold	
$ au_2$	$C_4 - C_6 - O_{10} - H_{12}$	2-fold	6 12
$ au_3$	$C_4 - C_7 - O_{13} - H_{14}$	2-fold	3 4
$ au_4$	$N_1 - C_4 - C_7 - O_{11}$	6-fold	
$ au_5$	$C_7 - C_4 - C_6 - O_{10}$	12-fold	
$ au_6$	$\mathrm{C}_6-\mathrm{C}_4-\mathrm{N}_1-\mathrm{H}_2$	12-fold	11

Table 1.2 Summary of the torsions considered by He and Allen for  $\alpha$ -serine.

<sup>a</sup> Red corresponds to oxygen, blue to nitrogen, grey to carbon, and white to hydrogen.

As mentioned in the introduction, the low vapour pressure and thermal instability of neutral amino acids, the first experimental identification of neutral  $\alpha$ -serine was not achieved until 2004 when Lambie *et al.* successfully observed four conformers of  $\alpha$ -serine through the use of MI-FTIR spectroscopy with an argon host matrix.<sup>19</sup> On the basis of the theoretical work performed by Gronert and O'Hair, they reoptimized the 12 most stable structures at the B3LYP/6-31++G\*\* level of theory and utilized scaled quantum mechanical force fields to predict the vibrational

frequencies. Identification of conformers 1, 2, 3, and 4 was achieved solely through comparison of the experimental spectrum with the predicted spectrum. As a result of this crude analysis, a number of conformers were likely missed during the assignment process. However, this article is significant in that it represents the first time neutral  $\alpha$ -serine was experimentally observed, which is an accomplishment in and of itself.

Shortly afterwards, Jarmelo *et al.* reported two separate MI studies on  $\alpha$ -serine.<sup>20,21</sup> In these reports they utilized isotopic substitution, and UV photoirradiation (200 nm) techniques to assess the conformational distribution of  $\alpha$ -serine in argon matrices, and its associated photoproducts. This enabled the assignment of 9  $\alpha$ -serine conformers, namely conformers 1 through 9. In addition, they identified ethanolamine, CO<sub>2</sub>, CO, H<sub>2</sub>O, and acetamide as the primary photoproducts. Interestingly, two, conformer dependent, photodissociation pathways were identified. Photolysis of conformers exhibiting OH … N hydrogen bonding between the alcohol side chain and amine group, yielded ethanolamine and CO<sub>2</sub> via decarboxylation. Whereas the photolysis of conformers exhibiting OH … N hydrogen bonding between the carboxyl hydrogen and amine group resulted in the formation of acetamide through the decarbonylation.

In 2007 Blanco *et al.* reported the assignment of seven  $\alpha$ -serine conformers through the use of laser-ablation microwave spectroscopy.<sup>22</sup> Namely, they identified conformers Ia, IIb, I'b, IIc, III<sub>β</sub>b, III<sub>β</sub>c, and IIa. For the sake of comparison, a table of conversion for nomenclature used in relevant studies on  $\alpha$ -serine has been included in the Appendix. The absence of two conformers which were identified by Jarmelo *et al.* was attributed to collisional cooling during the supersonic expansion. This publication represents the first experimental identification of neutral  $\alpha$ -serine achieved with laser ablation.

Lastly, in 2015 Najbauer *et al.* coupled MI-FTIR spectroscopy with selective near-infrared (NIR) irradiation to identify eight conformers of  $\alpha$ -serine.<sup>23</sup> Namely, these conformers are 1 through 7 and 10. An argon matrix was utilized for the identification of conformers 1 through 6, with conformers 7 and 10 being confirmed through the use of a nitrogen matrix, which is known to stabilize unstable conformers. That being said, conformers 7 and 10 were assigned to the same experiment bands, hence, only conformer 7 or 10 was assigned as opposed to both. This assignment contradicts those made by Jarmelo *et al.*, and as such, the goal of this thesis is to identify the configurations of  $\alpha$ -serine present in a solid parahydrogen matrix.

#### **1.1.2.** Introduction to $\alpha$ -alanine

 $\alpha$ -alanine, being only larger than glycine, is the second smallest biologically relevant amino acid and the smallest chiral amino acid. Since this thesis is primarily interested in the excited states of  $\alpha$ -alanine, the identification of conformers will only be briefly introduced. There have been many investigations into the excited states of  $\alpha$ -alanine, and as such, only the two most relevant publications will be introduced.

Similar to  $\alpha$ -serine,  $\alpha$ -alanine has been the subject of many theoretical investigations, in fact, the first comprehensive investigation was published in 1995 by Gronert and O'Hair alongside their investigation of  $\alpha$ -serine.<sup>16</sup> In their study they identified ten stable configurations with HF/6-31G\*. Shortly afterwards in the same year, Cao *et al.* identified thirteen conformers of  $\alpha$ -alanine with MP2/6-31G\*\*.<sup>24</sup> In addition to that, Schäfer et al. utilized HF/6-311G\*\* to optimize all of the trial structures presented by Gronert and O'Hair, discovering an additional three stable configurations, for a total of thirteen. Hence, thirteen identical conformers were independently identified by Caro and Schäfer via MP2 and HF respectively. Shortly thereafter, Csázár et al. identified 13 stable configurations of  $\alpha$ -alanine at the MP2(full)/6-311++G\*\* level of theory and reported the CCSD(T) energies.<sup>25</sup> It appears that  $\alpha$ -alanine was a hot topic in the theoretical chemistry community during the years of 1995 and 1996, as all of these publications came out within a few months of one another. After 1996, not many theoretical investigations into the conformational landscape of  $\alpha$ -alanine were reported. However, in 2011 Balabin *et al.* reported a FPA on the conformers of  $\alpha$ -alanine identifying twelve stable configurations at the B3LYP/augcc-pVTZ level of theory.<sup>26</sup> Lastly, in 2010 Jaeger et al. optimized the two lowest energy conformers of  $\alpha$ -alanine at the CCSD(T)/cc-pVTZ level of theory, then subsequently utilized the FPA to determine their relative energies.<sup>27</sup> However, unlike Balabin, this publication is primarily concerned with determining the semiexperimental structures through the use of rotational constants obtained from microwave spectroscopic experiments.

In 2007, Maul *et al.* probed the electronic excitations for the 3 lowest energy conformers of  $\alpha$ -alanine through the use of gradient corrected (spin-) DFT with a projector-augmented wave scheme.<sup>28</sup> Interestingly, they predict that, upon irradiation with UV light,  $\alpha$ -alanine undergoes photodissociation. Although it is not explicitly stated, the resulting product structures provided within their publication are that of the hydrocarboxyl (HOCO) and ethylamine radicals.

Additionally, the HOCO radical is trans for conformers 1 and 2, and cis for conformer 3. Unlike the experimental investigation on  $\alpha$ -serine, the same photoproducts are predicted for the three conformers of  $\alpha$ -alanine. It is worth mentioning that this publication does not include any of the necessary details regarding the photodissociation process. However, as far as the author is aware, this is the only publication showing the photodissociation of  $\alpha$ -alanine.

In 2014 Tia *et al.* examined the photoionization of  $\alpha$ -alanine through the coupling of synchrotron radiation with a double imaging photoelectron coincidence spectrometer in the Vacuum UV (VUV) range.<sup>29</sup> Through the use of symmetry adapted cluster configuration interaction (SAC-CI) calculations, they determined the vertical ionization potentials to be 9.581, 9.668, and 9.593 eV for the first 3 conformers of  $\alpha$ -alanine. Additionally, they reported the presence of the HOCO radical at 9.17 eV, and the ethylamine radical at 9.48 eV. Sample deposition was obtained through the use of resistive heating and aerosol thermodesportion. Interestingly, the ethylamine radical was only detected in experiments utilizing the resistive heating technique, whereas the HOCO radical was detected in both.

#### **1.2. Matrix Isolation Spectroscopy**

#### 1.2.1. Fourier Transform Infrared Spectroscopy

Through the use of the Fourier Transform (FT) any waveform can be rewritten as a sum of sinusoidal functions. Recall that a waveform with a period of t/n is periodic at intervals of t. In short, the FT converts time-based waveforms into individual cycles, reporting the amplitude, offset, and rotation speed for each cycle. This will be touched upon after a brief introduction to the Michelson interferometer.

The Michelson interferometer functions to modulate optical radiation. In short, the Michelson interferometer consists of a beam splitter, travelling mirror, and stationary mirror. An incoming beam of radiation is split via the beam splitter into two beams of nearly equal power and intensity. One beam is directed towards the stationary mirror, while the other to the travelling mirror. Upon reflection at the mirrors the twin beams recombine at the beam splitter, in such a way that changes in intensity can be measured as a function of the difference in the distance travelled by each beam. In other words, the travelling mirror serves to fluctuate the power incident on the detector in a reproducible manner. For example, when the travelling and stationary mirrors are

equal distance from the beam splitter (same path length), the split beams are said to be in phase and the resultant recombined beam is at the maximum signal power. Hence, differences in signal power at the detector are a function of the difference in path length, termed retardation. Plotting power against retardation yields an interferogram, which is a periodic function, and as such, can be analyzed with the FT. In brief, compared to conventional dispersive spectrometers, FT spectrometers yield higher signal power, signal-to-noise ratios, and higher resolution as a result of the multiplex advantage.

Additional improvements can be achieved through the use of multiple interferometers, in which the additional interferometers serve to improve spectral quality through indirect measurements, as opposed to directly interacting with the source light. For example, most high-resolution FTIR spectrometers contain a laser-fringe reference system, in which a helium-neon (HeNe) laser is utilized to regulate the travelling mirror. Briefly, monochromatic sources, such as lasers, produce cosine interferograms as maximum power is always achieved when retardation is zero, which can be utilized to regulate the oscillation speed of the travelling mirror. Additionally, one could include a white-light system for the purpose of triggering data sampling. Unfortunately, the maximum resolution attainable by FTIR spectrometers is limited by the travelling mirror. That is, resolution is primarily determined by the step-size of the travelling mirror, putting a physical limit on the attainable resolution. One method to overcome this is through the use of a dual frequency comb spectrometer, in which, the resolution is determined by difference in wavelengths of the two frequency combs.<sup>30</sup> Thereby, enabling one to attain resolutions equal to the line-width of the employed combs.

#### **2. Experimental and Computational Methods**

#### 2.1. Matrix Isolation FTIR Spectroscopy

#### 2.1.1. Matrix Isolation Chamber

An in-house built doubly shielded cryogenic chamber was utilized for all the experiments presented in this thesis. The chamber is composed of a stainless-steel outer shell with inner and outer diameters of 20 and 22 cm respectively. Inside the chamber, a copper cold plate, which is 10 cm in diameter, has the sole responsibility of housing the BaF<sub>2</sub> wedged window above the cold head. The cryostat utilized in this apparatus is capable of cooling the cold plate to 3.6 K, thereby cooling the window to ca. 4 K. A closed-cycle Gifford-McMahon refrigerator is utilized to cool the cold head. The BaF<sub>2</sub> wedge window is 25 mm in diameter with a thickness of 2 mm (mean) and is attached to the cold plate with a 4 by 4 cm copper window holder. The temperature of the chamber was monitored through the use of two silicon diode temperature sensors, which were attached to the cold plate and wedged window. In all experiments the chamber was kept at roughly  $3 \times 10^{-8}$  torr through the combined effects of a turbo molecular pump, which is capable of attaining pressures of  $3 \times 10^{-6}$  torr, and the cold head which acts as a cryopump. Like cryopumps, the cold head is capable of "removing" water vapour at four times the rate turbomolecular pumps are.

#### 2.1.2. Production of Enriched Parahydrogen Gas

Enriched parahydrogen gas was produced from normal hydrogen gas (99.99%, Praxair Canada Inc.) through the use of an inhouse-built converter. The converter was constructed by Dr. Takamasa Momose, alongside associates from the University of Illinois and University of British Columbia.<sup>31</sup> Unlike other parahydrogen converters, which reach cryogenic temperatures through the use of liquid  $N_2$  or  $H_2$  cryogens, this one utilizes a closed cycle He cryostat (liquid He cryogen).<sup>32</sup> The cold head has been modified to attach a reactor coil onto it, which is composed of oxygen free high conductivity copper. Briefly, conversion from ortho to parahydrogen is catalyzed through the use of 3.3 grams of hydrous ferric oxide catalyst (30 x 50 mesh), which is positioned inside the copper tubing.

#### **2.1.3. Deposition and Sublimation**

Deposition of parahydrogen onto the window was accomplished through the use of steel inlet tubing with a diameter of 1.59 mm, positioned 45° and 3.5 cm from the window. Flow rate of parahydrogen gas was controlled with a gas flow controller. Whereas deposition of solid samples is performed directly from the tip of the Knudsen cell, which is positioned 45° and 2.5 cm from the window. The fact that the matrix gas and sample inlets are both situated 45° from the window ensures that the two beams intersect at a 90° angle immediately in front of the window, ensuring ample mixing of the two gases. Prior to deposition in the experiments presented in this thesis, the window was cooled to 4 K. It is worth noting that the temperature of the window increases upon deposition of a gas simply due to the temperature of the gas being greater than that of the window.

The Knudsen cell used in these experiments was built in-house and is similarly designed to standard resistance-heated Knudsen cells. The cell itself is composed of a 42 by 8 mm copper cell body, and an 18 by 1.6 mm copper nozzle. It is worth noting that the nozzle diameter is 1 mm. Heating is achieved through the use of a ceramic heater attached to the rear of the cell and was powered with a standard DC power supply. The temperature was accurately monitored through the use of a solid state NTC thermistor sensor capable of reporting temperatures with an accuracy of  $\pm 1$  K, placed directly behind the sample compartment. Due to the positioning of the sensor directly behind the sample compartment, one can only report the temperature directly beside the sensor. That is, the temperature of the entire sample compartment is unknown. However, due to the small size of the sample compartment and the fact that no extreme temperatures were utilized, it is unlikely that the temperature greatly deviates from one side of the compartment to the other. Additionally, the experiments investigating conformational dependence on sublimation temperature are more concerned with the relative temperature than the absolute temperature. That is, the point of modulating the sublimation temperature is to see a change in the relative intensity of peaks, which corresponds to a change in conformational distribution that can be predicted from theory and used to support the spectral assignment. Hence, this non-uniformity in temperature, and the inability of the experimental apparatus to measure the non-uniformity, will not have any effect on the results presented in this thesis.

#### 2.1.4. FTIR Spectrometer and Measurements

The FTIR employed in the experiments presented here is a Bruker IFS 125HR high-resolution spectrometer that is equipped with a KBr beam splitter, globar MIR source, and a reference He-Ne laser. The spectrometer itself is kept at an approximate pressure of  $3 \times 10^{-2}$  torr to maximize the intensity of IR light irradiated onto the sample and is accomplished through the use of a standard mechanical pump. A parabolic mirror was used to deflect the IR light into the matrix isolation chamber and thereby onto the sample. BaF<sub>2</sub> windows with identical measurements to the sample window, were utilized to allow the IR beam to travel into and out of the matrix isolation chamber. Upon exiting the chamber, an additional parabolic mirror was used to deflect the beam into the liquid N<sub>2</sub> cooled MCT detector situated in a separate optic chamber, which was kept at a pressure similar to that of the spectrometer. All spectra presented in this thesis were recorded with a resolution of 0.1 cm<sup>-1</sup>.

#### 2.2. Electronic Structure Theory

Throughout the past century (ca. 1920 - 2020) the application of quantum chemistry to research has exploded from a relatively small group of theorists to being utilized in most chemistry research laboratories. For instance, synthetic chemists commonly apply quantum chemistry for the rationalization and prediction of reaction pathways, spectroscopists use it to aid in spectral analysis, and pharmaceutical chemists apply it to drug discovery.<sup>33</sup> The widespread use and advancement of quantum chemistry can largely be attributed to two factors: (1) rapid development of computational hardware (and the associated reduction in cost), and (2) the introduction of "black box" methods for predicting molecular properties.<sup>33,34,35</sup> A black box method is a one that can be easily performed with little to no knowledge of the programs' inner-workings. However, the utilization of these black box methods does not come without cost. This is made abundantly clear by the frequent use of the B3LYP functional<sup>36,37</sup> in the prediction of organic chemical reactions. Since 2007, multiple independent studies have shown that the B3LYP functional, without any empirical dispersion corrections, fails to qualitatively and quantitatively describe organic reaction pathways, and the associated thermochemistry for many organic reactions.<sup>38,39,40,41</sup> Regardless of these findings, the B3LYP functional is still widely used as the sole theoretical basis supporting experimental results, often resulting in the publication of erroneous information.<sup>34</sup> It is important to note that the B3LYP functional does not fail for every organic molecule. In fact, it describes the

ground state potential energy surface of some amino acids quite accurately.<sup>25</sup> As such, when using any approximate quantum chemical method, it is of the utmost importance to employ at least two different techniques to confirm the validity of the theoretical results. When quantum chemistry is applied to molecular spectroscopy, this is typically accomplished through the use of both density functional theory, and Møller-Plesset perturbation theory.

The widespread misuse of the B3LYP functional noted above, is largely a result of users not understanding the inner workings of the technique and as such, they do not realize its shortcomings. Due to the complexity of the analyses discussed in this thesis, it is necessary for one to fully understand the techniques applied, as opposed to treating them as a black box. As such, this section aims to briefly introduce the reader to the computational techniques employed for the ground state analysis of  $\alpha$ -serine. In particular, the Hartree-Fock (HF)<sup>42,43</sup> method, density functional theory (DFT),<sup>44</sup> Møller-Plesset (MPn) perturbation theory,<sup>45</sup> and coupled cluster theory (CC)<sup>46,47</sup> will be discussed. Additionally, it is worth mentioning that explicit electron correlation in coupled cluster theory,<sup>48</sup> and empirical dispersion corrections in DFT, particularly with the B3LYP functional,<sup>49</sup> were utilized within this thesis but will not be discussed here. Note that a description of the computational techniques used in the excited state analysis of  $\alpha$ -alanine can be found in the following section of this thesis (Section 2.3). The equations shown in the following sections, were sourced from Frank Jensen's Introduction to Computational Chemistry textbook, with additional references being provided when required.<sup>55</sup>

#### 2.2.1. Hartree-Fock Theory

Electronic structure theory aims to describe the motion of electrons within atoms and molecules most commonly via the time-independent Schrödinger equation,

$$\widehat{H}|\Psi_n\rangle = E_n|\Psi_n\rangle,\tag{2.1}$$

where  $\hat{H}$ ,  $\Psi_n$ , and  $E_n$  are the Hamiltonian operator, wavefunction, and energy eigenstate respectively. The Hamiltonian operator for a given system corresponds to the total energy of that system. Hence, the molecular Hamiltonian, also called the Coulomb Hamiltonian, represents the kinetic and potential energy of all electrons, nuclei, and their interactions. In atomic units, the molecular Hamiltonian is given by the following expression,

$$\widehat{H} = \underbrace{-\sum_{i} \frac{1}{2} \nabla_{i}^{2}}_{\widehat{T}_{e}} \underbrace{-\sum_{A} \frac{1}{2M_{A}} \nabla_{A}^{2}}_{\widehat{T}_{n}} \underbrace{+\sum_{i>j} \frac{1}{|\mathbf{r}_{i} - \mathbf{r}_{j}|}}_{\widehat{V}_{ee}} \underbrace{-\sum_{i,A} \frac{Z_{A}}{|\mathbf{r}_{i} - \mathbf{R}_{A}|}}_{\widehat{V}_{ne}} \underbrace{+\sum_{A>B} \frac{Z_{A}Z_{B}}{|\mathbf{R}_{A} - \mathbf{R}_{B}|}}_{\widehat{V}_{nn}}.$$
(2.2)

Kinetic energy operators for electrons and nuclei are  $\hat{T}_e$  and  $\hat{T}_n$  respectively, whereas  $\nabla_i^2$  and  $\nabla_A^2$  denote the Laplacian with respect to electronic,  $\mathbf{r}_i$ , and nuclear,  $\mathbf{R}_A$ , coordinates.  $\hat{V}_{ee}$ ,  $\hat{V}_{nn}$ , and  $\hat{V}_{ne}$ , are the potential energy operators corresponding to the Coulombic interactions between electrons, nuclei, and electrons and nuclei respectively. Lastly,  $Z_A$  and  $M_A$  denote the charge and mass of nuclei A in atomic units.<sup>50</sup> It is worth mentioning that the above equation is non-relativistic, hence, it does not account for relativistic effects such as the relativistic mass, spin-orbit coupling, and the parity violation in chiral molecules. No relativistic calculations were performed within this thesis, and as such, no comments regarding the inclusion of relativistic effects will be made, with the exception of mentioning the article published by Wenjian Liu in 2020, which is a good reference for anyone interested in the subject.<sup>51</sup>

Solving the full molecular Hamiltonian, Equation (2.2), is currently infeasible for molecules of any size. In response to this a number of approximations will be made to simplify the Hamiltonian into one that we can solve. It is here that the Born-Oppenheimer (BO) approximation first comes into play.<sup>52</sup> The BO approximation is a central assumption to molecular spectroscopy, and its origins can be found in the fact that electrons are substantially lighter than nuclei. On the basis of this mass difference, it is reasonable to assume that electron velocity is much greater than that of nuclei, and as such it can be said that, from the perspective of the nuclei, electrons adjust to any change in nuclear coordinates instantaneously.<sup>53</sup> As a result of this it is possible to decouple the electron and nuclear terms in the molecular Hamiltonian, resulting in an electronic and nuclear Hamiltonian. Respectively, the electronic and nuclear Hamiltonians have the form,

$$\widehat{H}_{e} = \underbrace{-\sum_{i} \frac{1}{2} \nabla_{i}^{2}}_{\widehat{T}_{e}} \underbrace{+\sum_{i>j} \frac{1}{|\mathbf{r}_{i} - \mathbf{r}_{j}|}_{\widehat{V}_{ee}}}_{\widehat{V}_{ee}} \underbrace{-\sum_{i,A} \frac{Z_{A}}{|\mathbf{r}_{i} - \mathbf{R}_{A}|'}}_{\widehat{V}_{ne}},$$
(2.3)

and,

$$\widehat{H}_{n} = \underbrace{-\sum_{A} \frac{1}{2M_{A}} \nabla_{A}^{2}}_{\widehat{T}_{n}} \underbrace{+\sum_{A > B} \frac{Z_{A} Z_{B}}{|\mathbf{R}_{A} - \mathbf{R}_{B}|}}_{\widehat{V}_{nn}} \underbrace{+E_{e}(\mathbf{R})}_{\text{From 2.6}}.$$
(2.4)

Under the BO approximation the total wavefunction,  $\Psi$ , is given by the product of the nuclear,  $\psi_n$ , and electronic,  $\psi_e$ , wavefunctions:

$$\Psi(\mathbf{R},\mathbf{r}) = \psi_n(\mathbf{R})\psi_e(\mathbf{r},\mathbf{R}). \tag{2.5}$$

It is interesting to note that the nuclear wavefunction depends only on nuclear coordinates, but the electronic wavefunction depends on electronic and nuclear coordinates. The electronic wavefunctions dependence on nuclear coordinates is commonly interpreted as being parametrically dependent on electron – nuclei separation distances arising from the  $\hat{V}_{ne}$  term in Equation (2.3). Substituting the electronic Hamiltonian and wavefunction into the Schrödinger equation gives the following expression,

$$\widehat{H}_e \psi_e(\mathbf{r}, \mathbf{R}) = E_e(\mathbf{R}) \psi_e(\mathbf{r}, \mathbf{R}).$$
(2.6)

Where the electronic energy is given by  $E_e$  and its dependence on nuclear position is the underlying basis of the adiabatic potential energy surface (PES), which is a central concept in molecular spectroscopy.<sup>54</sup> The nuclear Schrödinger equation describes the rotational, vibrational, and translational motion of the nuclei, and can be obtained in a fashion identical to that done for the electronic Schrödinger equation,

$$\widehat{H}_n \psi_n(\mathbf{R}) = E_n \psi_n(\mathbf{R}). \tag{2.7}$$

Hence, the electronic energies, as a result of their parametric dependence on nuclear geometry, provide a potential on which the nuclei can move.

As a result of the two-electron Coulombic potential term in the electronic Hamiltonian,  $\hat{V}_{ee}$ , Equation (2.6), obtaining an exact solution to the electronic Schrödinger equation for any molecule with more than one electron completely infeasible. That being the case we can approximate the two-electron potential as a sum of one-electron terms, making the Hamiltonian solvable for molecules with more than a single electron. A few different approaches to this approximation exist, however, the most popular method is termed the Hartree approximation.<sup>42</sup> In this approximation the two-electron potentials are approximated through the use of a mean field, thereby allowing the total electronic wavefunction to be represented as the product of one-electron spatial orbitals.<sup>42,54,55</sup> That is, it is assumed that the electrons in a given system are independent and interact only through a mean electric field, making each potential term dependent on the coordinates of a single electron as opposed to the coordinates of every electron. This method is also referred to as the mean field approximation since the individual fields are replaced by a mean field. It is worth noting that Hartree approximated the electronic wavefunction as simple one-electron wavefunctions.

In order to appropriately represent the wavefunction as a product of one-electron spatial orbitals, one should recall that the total electronic wavefunction must adhere to the Pauli principle.

Additionally, since electrons are fermions, the wavefunction must be antisymmetric upon exchange.<sup>54</sup> This is accomplished through the product of a spatial orbital  $\psi_i(\mathbf{r})$  and a spin function. As mentioned above, electrons are fermions, so spin can be either  $+\frac{1}{2}$  or  $-\frac{1}{2}$ . The resulting wavefunction from this product is termed the spin orbital,  $\chi_i(\mathbf{k})$ , which is a function of the electrons spatial and spin coordinates,  $\mathbf{r}$  and  $\sigma$ , respectively:

$$\chi_i(k) = |i\rangle = \chi_i(\mathbf{r}_k, \sigma_k). \tag{2.8}$$

In other words, each one-electron spatial orbital generates two orthonormal spin orbitals that are a function of the electrons spatial and spin coordinates. Note that spin orbitals are sometimes referred to as molecular orbitals. Since each spatial orbital generates two spin orbitals, there will always be more spin orbitals than there are electrons to fill them. It is standard to refer to the unoccupied spin orbitals as virtual orbitals. Recall that the electronic wavefunction must also be antisymmetric upon exchange, which is defined as  $\psi(a, ..., b, ..., n) = -\psi(b, ..., a, ..., n)$ . This condition is met by constructing the total electronic wavefunction from the antisymmetrized product of spin orbitals. That is, the electronic wavefunction can be constructed as a Slater determinant of *n* orthonormal spin orbitals  $\chi_i$ ,

$$\psi_e(1,2,\cdots,n) = \frac{1}{\sqrt{n!}} \det \begin{vmatrix} \chi_1(1) & \cdots & \chi_1(n) \\ \vdots & \ddots & \vdots \\ \chi_n(1) & \cdots & \chi_n(n) \end{vmatrix}.$$
(2.9)

It is worth mentioning that through the procedure for creating spin orbitals and taking their antisymmetrized product, the Pauli Exclusion principle is automatically satisfied.<sup>56</sup> The use of the above wavefunction was discovered by Fock whom improved upon Hartree's simple one-electron wavefunction by accounting for electron antisymmetry.

The Hartree-Fock energy can be calculated by substituting the electronic Hamiltonian and wavefunction, Equations (2.3) and (2.9), into the Schrödinger equation, which yields the following expression for the HF energy,  $E_{\rm HF}$ ,

$$E_{\rm HF} = \langle \psi_e | \hat{H}_e | \psi_e \rangle = \sum_i \langle i | \hat{h} | i \rangle + \frac{1}{2} \sum_{ij} (\langle ij || ji \rangle), \qquad (2.10)$$

where  $\hat{h}$  contains the kinetic energy,  $\hat{T}_e$ , and electron-nuclei,  $\hat{V}_{ne}$ , interaction terms via integration over the electronic spatial and spin coordinates,

$$\langle i|\hat{h}|i\rangle = \int \chi_i^*(1) \underbrace{\left[\frac{1}{2}\nabla_i^2 - \sum_A \frac{Z_A}{|\mathbf{r}_i - \mathbf{R}_A|}\right]}_{\hat{h}(i)} \chi_i(1) d\tau_k = h_{ii}, \qquad (2.11)$$

where  $\tau_k$  represents the spatial and spin coordinates of electron k. Whereas the antisymmetrized integrals,  $\langle ij|ij \rangle - \langle ij|ji \rangle = \langle ij||ji \rangle$ , refer to the Coulomb and exchange interaction,

$$\langle ij|ij \rangle = \int d\tau_1 \chi_i^*(1) \underbrace{\int d\tau_2 \chi_j^*(2) \frac{1}{r_{12}} \chi_j(2) \chi_i(1)}_{\hat{j}_j(1) \chi_i(1)}, \qquad (2.12)$$

and,

$$\langle ij|ji\rangle = \int d\tau_1 d\sigma_1 \chi_i^*(1) \underbrace{\int d\tau_2 \chi_j^*(2) \frac{1}{r_{12}} \chi_i(2) \chi_j(1)}_{\hat{K}_j(1)\chi_i(1)}.$$
(2.13)

In the above expressions the Coulomb and exchange operators are  $\hat{J}_j$  and  $\hat{K}_j$  respectively. Combining the above two equations:

$$\langle ij || ji \rangle = \int d\tau_1 \chi_i^*(1) \hat{J}_j(1) \chi_i(1) - \int d\tau_1 \chi_i^*(1) \hat{K}_j(1) \chi_i(1).$$
(2.14)

The exchange contribution arises from the indistinguishability of electrons, whereas the Coulomb contribution arises from the mean-field approximation previously discussed in this section.

Minimization of the HF energy is achieved through Self Consistent Field theory, see Algorithm 1 of the Appendix A, which is a variational method for solving the HF energy by means of optimizing the molecular orbitals. This requires the molecular orbitals to be orthonormal,

$$\int d\tau_1 \chi_i^*(1) \,\chi_i(1) = \delta_{ij}.$$
(2.15)

It can be shown that application of the variational procedure leads to the Hartree-Fock equation,

$$\widehat{F}\chi_{i} = \left[\widehat{h} + \sum_{j} (\widehat{J}_{j} - \widehat{K}_{j})\right]\chi_{i} = \epsilon_{i}\chi_{i}, \qquad (2.16)$$

where  $\hat{F}$  is the Fock operator and  $\epsilon_i$  are the orbital energies. It is worth mentioning that the Fock operator is a one-electron operator that depends on the molecular orbital  $\chi_i$ . It is useful to define the one-electron HF potential operator as  $\hat{v}_{HF}$ , which from Equation (2.16) is:

$$\hat{\nu}_{HF} = \sum_{i}^{n} (\hat{J}_{i} - \hat{K}_{i}), \qquad (2.17)$$

where i represents the orbital and n is the total number of occupied orbitals.

The HF energy can, theoretically, be calculated directly from Equation (2.10). However, doing so requires numerical integration along a finely spaced three-dimensional grid, making it infeasible for a molecule with more than a few electrons. In the 1950s Roothaan<sup>57</sup> and Hall<sup>58</sup> discovered that the HF equation can be represented as a set of matrix equations by expanding the spatial orbitals into a basis of atomic orbitals (AO), thereby, reducing the HF equation to a single matrix eigenvalue problem that can routinely solved. Expansion of the spatial component,  $\chi_i$ , for each spin orbital in a Slater determinant of a finite basis set, { $\phi_i$ }, is given by:

$$\chi_i = \sum_n C_{in} \phi_n , \qquad (2.18)$$

where  $C_{ij}$  is the expansion coefficient for spin orbital *j*. The expansion coefficients are determined through the HF-SCF procedure. It is now convenient to define the density matrix as:

$$\mathbf{D}_{nm} = \sum_{i} 2C_{ni}^* C_{mi}.$$
(2.19)

From this, the HF energy can be written as:

$$E_{\rm HF} = \sum_{\mu\nu} D_{\mu\nu} h_{\mu\nu} + \frac{1}{2} \sum_{\mu\nu\rho\sigma} D_{\mu\nu} D_{\rho\sigma} \left( \langle \mu\rho | \nu\sigma \rangle - \frac{1}{2} \langle \mu\rho | \sigma\nu \rangle \right).$$
(2.20)

Operating on the expanded basis set with the Fock operator, Equations (2.16) and (2.18), followed by projection onto the basis set yields the Roothaan-Hall equations:

$$\sum_{\nu} \underbrace{\left(h_{\mu\nu} + \sum_{\rho\sigma} D_{\rho\sigma}(\langle \mu\rho | \nu\sigma \rangle - \frac{1}{2} \langle \mu\rho | \sigma\nu \rangle\right)}_{F_{\mu\nu}} C_{\nu i} = \sum_{\nu} \underbrace{\langle \phi_{\mu} | \phi_{\nu} \rangle}_{S_{\mu\nu}} C_{\nu i} \varepsilon_{i}.$$
(2.21)

Where  $F_{\mu\nu}$  and  $S_{\mu\nu}$  are the Fock and overlap matrix elements. The resulting eigenvectors and eigenvalues represent the expansion coefficients  $C_{\nu i}$  and orbital energies  $\varepsilon_i$  respectively. It is worth noting that only the restricted HF procedure for closed shell molecules is shown.<sup>33</sup>

With this method, the HF-SCF procedure is variational in the density matrix, during which the HF energy is minimized through the optimization of the basis set expansion coefficients. The full algorithm is shown in the Appendix, however, in short, one inputs an initial guess  $D_0$  for the density matrix, substituting the guess into the Roothaan-Hall equations yields a new matrix  $D_1$ which is typically closer to the true solution. With each iteration one is able to improve the molecular orbital coefficients, thereby reducing the energy. The procedure is said to have converged when the input coefficients are equal to the output coefficients. Since the procedure is variational in nature, the current energy is always greater than the exact ground state energy:

$$E_{exact} \le E_{\rm HF}.\tag{2.22}$$

The two-electron interaction in Equation (2.14) treats the exchange interaction correctly. However, in HF theory the motion of an electron is described based on the mean field of all other electrons, as opposed to true  $r_{ij}^{-1}$  repulsion energy. As a result of this approximation, HF theory completely neglects the correlational component of the Coulomb interaction. Correlation energy,  $E_{corr}$ , is defined as the difference of the exact non-relativistic energy and the HF energy,

$$E_{corr} = E_{exact} - E_{HF}.$$
 (2.23)

Since dispersion forces arise from electron correlation, systems where van der Waals interactions play a significant role, such as non-covalently bound molecular complexes and complexes with substantial intramolecular hydrogen bonding, cannot be accurately depicted by HF theory.<sup>59</sup> One can correct for electron correlation variationally or through the application of perturbation theory. The most popular method for this is Møller-Plesset perturbation theory, which is discussed in the sub-section below.

#### **2.2.2. Møller-Plesset Perturbation Theory**

In the following section, little effort has been made to explain the general procedure for manybody perturbation theory, rather, the author directs the reader to a review article in the International Journal of Quantum Chemistry as an excellent reference on the topic.<sup>60</sup> Møller-Plesset perturbation theory (MPn) is a special case of Rayleigh-Schrödinger perturbation theory, where the zerothorder Hamiltonian is chosen to be the HF Hamiltonian, previously denoted as the Fock operator.<sup>45</sup> The total Hamiltonian for any perturbative method is simply the sum of an unperturbed (zeroth order) Hamiltonian, and a perturbed Hamiltonian,

$$\widehat{H} = \widehat{H}^{(0)} + \lambda \widehat{H}', \qquad (2.24)$$

where  $\hat{H}^{(0)}$ ,  $\hat{H}'$ , and  $\lambda$  is the unperturbed, and perturbed Hamiltonian, and perturbation parameter, respectively.<sup>45</sup> Recall that the zeroth order Hamiltonian for MPn theory is the HF Hamiltonian,

$$\hat{H}^{(0)} = \hat{F}.$$
 (2.25)

Whereas the perturbed Hamiltonian,  $\hat{H}'$ , is defined as the difference between the electron-electron Coulomb and HF potentials,

$$\widehat{H}' = \widehat{H} - \widehat{H}_0 = \frac{1}{2} \sum_{i>j}^n \frac{1}{|\mathbf{r}_i - \mathbf{r}_j|} - \sum_i^n \widehat{v}_{HF}(\mathbf{r}_i) = \sum_{i>j} \left( \frac{1}{|\mathbf{r}_i - \mathbf{r}_j|} - \widehat{v}_{HF}(\mathbf{r}_i) \right), \quad (2.26)$$

From this it is evident that the perturbative term describes the correlation energy, and as such, the more terms considered in the perturbation, the more accurate the correlation energy will be. Additionally, it is worth mentioning that the wavefunction,  $\Phi$ , and energy, *E*, are expanded as a perturbative series in  $\lambda$ ,

$$\Phi_n = \lim_{n \to \infty} \sum_{i=0}^n \lambda^i \Phi_n^i, \qquad (2.27)$$

with energy being given by,

$$E_n = \lim_{n \to \infty} \sum_{i=0}^n \lambda^i E_n^i.$$
(2.28)

Recall that the unperturbed Hamiltonian is the Fock operator, it follows that the zeroth order wavefunction for the ground state is a single HF determinant,  $\Phi_0$ , and the excited state wavefunctions are given by their respective excited determinants,  $\Phi_n$ . That is,  $\Phi_a^r$  corresponds to the one electron, *a*, excitation from an occupied orbital, *r*, to some higher energy unoccupied orbital. Additionally,  $\Phi_{ab}^{rs}$  and  $\Phi_{abc}^{rst}$  represent the double excitation of electrons *a*, *b*, and triple excitation of electrons *a*, *b*, and *c* respectively. The ground state zeroth order energy,  $E_0^{(0)}$ , is simply the sum of all occupied orbitals energies,

$$E_0^{(0)} = \sum_a^n \epsilon_a, \qquad (2.29)$$

where n is the number of occupied orbitals.

First order corrections, known as MP1, or more commonly, HF, to the energy are easily obtained as expectation values of the HF determinant over the perturbative operator,

$$E_{0}^{(1)} = \langle \Phi_{0} | \hat{H}' | \Phi_{0} \rangle = -\frac{1}{2} \sum_{a,b}^{n} \langle ab || ab \rangle.$$
(2.30)

From standard perturbation theory, the total first order energy is simply the sum of the zeroth energy and the first order correction,

$$E_0^{(0)} + E_0^{(1)} = \sum_{a}^{n} \epsilon_a - \frac{1}{2} \sum_{a,b}^{n} \langle ab \| ab \rangle = E_0^{HF}.$$
 (2.31)

A quick comparison with Equation (2.10) verifies that the first order corrected energy is equal to the HF energy.

Second order corrections, known as MP2, are obtained via the expression,

$$E_0^{(2)} = -\sum_{n \neq 0} \frac{\left| \left\langle \Phi_0 \left| \hat{H}' \left| \Phi_n \right\rangle \right|^2}{E_n^{(0)} - E_0^{(0)}},$$
(2.32)

where  $\Phi_n$  denotes single, double, triple, and higher excited determinants. However,  $\hat{H}'$  is a twobody operator, and as such, any excitation with respect to  $\Phi_0$  involving more than two-bodies yields vanishing matrix elements. That is, one need only consider single and double excited determinants, greatly simplifying Equation (2.32). Further simplification arises from the fact that single excitations also yield vanishing matrix elements:

$$\left\langle \Phi_{0} \middle| \widehat{H}' \middle| \Phi_{a}^{r} \right\rangle = \sum_{b}^{n} \langle ab \| rb \rangle - \langle a | \hat{v}_{HF} | r \rangle = \sum_{b}^{n} \langle ab \| rb \rangle - \sum_{b}^{n} \langle ab \| rb \rangle = 0.$$
(2.33)

Thus, the second order contribution to energy only requires consideration of the doubly excited determinants,  $\Phi_{ab}^{rs}$ , which simplifies Equation (2.32) to:

$$E_0^{(2)} = -\sum_{a < b}^n \sum_{r < s}^m \frac{|\langle ab \| rs \rangle|^2}{\epsilon_r + \epsilon_s - \epsilon_a - \epsilon_b},$$
(2.34)

where *n* and *m* correspond to the occupied and unoccupied orbitals respectively. Furthermore, recall the antisymmetry requirement for the integral's states that  $\langle ab || rs \rangle = -\langle ab || sr \rangle = -\langle ba || rs \rangle$ , and  $\langle ab || rs \rangle = 0$  if a = b or r = s. Applying these properties to Equation (2.34) yields an even simpler expression,

$$E_0^{(2)} = -\frac{1}{4} \sum_{a,b}^n \sum_{r,s}^m \frac{|\langle ab \| rs \rangle|^2}{\epsilon_r + \epsilon_s - \epsilon_a - \epsilon_b}.$$
(2.35)

Thus, the ground state total MP2 energy is given by the sum of all contributions,

$$E_0^{MP2} = E_0^{(0)} + E_0^{(1)} + E_0^{(2)} = E_0^{HF} + E_0^{(2)}.$$
 (2.36)

It is worth mentioning that the second order correction to the energy is always negative, and since this method is not variational, the MP2 total energy is not necessarily greater than the true energy. Additionally, MPn theory fails for systems with no (or an infinitely small) HOMO-LUMO gap, as  $\epsilon_r + \epsilon_s - \epsilon_a - \epsilon_b = 0$  causing second order corrections to diverge to negative infinity. In theory, one could calculate an infinite number of corrections to the energy, yielding the true energy. However, with each additional term, the computational cost increases exponentially. Additionally, with each additional term the correction to the energy decreases. That is, if one assumes that the HF energy contains 99% of the systems energy, then second order corrections will account for 0.6%, third order corrections accounting for 0.2%, fourth order corrections account for 0.05%, and so forth. As such, due to the steep increase in computational cost, truncating after the second correction is most commonly used.<sup>55</sup> That is, MP2 is substantially more popular than all other forms of MPn theory, such as MP3, MP4, and so forth. In this thesis calculations were only performed up to MP2, and as such, the inclusion of the additional terms would be irrelevant.

#### 2.2.3. Coupled Cluster Theory

Unlike the methods discussed in the above subsections, the coupled cluster (CC) wavefunction can trace its origins to an exponential *ansatz*:

$$\Psi_{CC}\rangle = e^{\hat{T}}|\Psi_0\rangle, \qquad (2.37)$$

where  $\Psi_0$  is typically the HF wavefunction, and  $\hat{T}$  is an excitation operator typically referred to as the cluster operator. The total cluster operator is obtained from the sum of cluster operators of different excitation levels,

$$\hat{T}_n = \sum_{i}^{n} \hat{T}_i = \hat{T}_1 + \hat{T}_2 + \dots + \hat{T}_n, \qquad (2.38)$$

where *i* denotes the number of electrons excited from occupied to unoccupied orbitals. That is,  $\hat{T}_1$  considers all single electron excitations,  $\hat{T}_2$  considers all double electron excitations, and so forth.<sup>55</sup> The single excitation operator, in the second quantization formalism, has the following form,

$$\hat{T}_{1} = \sum_{a}^{n} \sum_{i}^{n} t_{a}^{i} \,\hat{a}_{i}^{\dagger} \hat{a}_{a}, \qquad (2.39)$$

where  $\hat{a}_i^{\dagger}$  and  $\hat{a}_a$  are the annihilation and creation operators for the spin orbitals *i* and *a*, respectively. Additionally, the cluster amplitudes to be determined are given by  $t_a^i$ . Additionally, the second excitation operator in the second quantization formalism is,

$$\hat{T}_{2} = \sum_{a < b}^{n} \sum_{i < j}^{n} t_{ab}^{ij} \,\hat{a}_{i}^{\dagger} \hat{a}_{a} \hat{a}_{j}^{\dagger} \hat{a}_{b}.$$
(2.40)

Imposing the condition that the amplitudes,  $t_{ab}^{ij}$ , must be antisymmetric with respect to exchange, and recalling the anticommutation property for annihilation and creation operators,  $\hat{a}_a \hat{a}_b = -\hat{a}_b \hat{a}_a$ , the second excitation operator has the form,

$$\hat{T}_{2} = \frac{1}{4} \sum_{a,b}^{n} \sum_{i,j}^{n} t_{ab}^{ij} \,\hat{a}_{i}^{\dagger} \hat{a}_{a} \hat{a}_{j}^{\dagger} \hat{a}_{b}.$$
(2.41)

It is useful to generalize the cluster operator for up to *n*-tuple excitations,

$$\widehat{T}_n = \frac{1}{(n!)^2} \sum_{a,b,c\cdots}^n \sum_{i,j,k,\cdots}^n t_{abc\cdots}^{ijk\cdots} \widehat{a}_i^{\dagger} \widehat{a}_a \widehat{a}_j^{\dagger} \widehat{a}_b \widehat{a}_k^{\dagger} \widehat{a}_c \cdots.$$
(2.42)

Substituting Equation (2.37) into the Schrödinger equation yields:

$$\widehat{H}e^{\widehat{T}}|\Psi_{0}\rangle = Ee^{\widehat{T}}|\Psi_{0}\rangle.$$
(2.43)

An expression for the correlation energy can be obtained by subtracting the HF energy from both sides of the above equation:

$$\underbrace{\left(\widehat{H} - \left\langle \Psi_0 \middle| \widehat{H} \middle| \Psi_0 \right\rangle\right)}_{\widehat{H}_N} e^{\widehat{T}} |\Psi_0\rangle = \underbrace{\left(E - E_{HF}\right)}_{E_{corr}} e^{\widehat{T}} |\Psi_0\rangle, \tag{2.44}$$

where  $E_{corr}$  represents the correlation energy, and  $\hat{H}_N$  is the normal-ordered Hamiltonian operator. By definition, the Hamiltonian is constructed as a normal-ordered product of annihilation and creation operators, in which all annihilation operators are to the right of all creation operators, thereby the product, when applied to the vacuum state, is zero.<sup>55</sup> Contributions from one-electron terms in the normal-ordered Hamiltonian are given by the operator  $\hat{F}_N$ , whereas the operator  $\hat{W}_N$  contains the two-electron terms:

$$\widehat{F}_N = \sum_{ab} \mathbf{F}_{ab} \{ \widehat{a}_a^{\dagger} \widehat{a}_b \}, \qquad (2.45)$$

$$\widehat{W}_N = \frac{1}{4} \sum_{abij} \langle ab \| ij \rangle \{ \widehat{a}_a^{\dagger} \widehat{a}_b^{\dagger} \widehat{a}_i \widehat{a}_j \}.$$
(2.46)

The one electron operator,  $\hat{F}_N$ , is simply the Fock operator, and as such,  $\mathbf{F}_{ab}$  are the Fock matrix elements,

$$\mathbf{F}_{ab} = \langle a | \hat{h} | b \rangle + \sum_{i} \langle ai | | bi \rangle.$$
(2.47)

Solving these equations requires substantial computational effort, and as such, the CC equations are typically not solved variationally. However, the amplitudes for each excitation and their

contribution to the correlational energy can be obtained via multiplication from the left of Equation (2.44) with  $e^{-\hat{T}}$ , followed by projection onto the reference and excited determinants,

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$$\Delta E_{corr} = \left\langle \Psi_0 \middle| e^{-\hat{T}} \widehat{H}_N e^{\hat{T}} \middle| \Psi_0 \right\rangle \tag{2.48}$$

$$\left\langle \Psi_i^a \middle| e^{-\hat{T}} \hat{H}_N e^{\hat{T}} \middle| \Psi_0 \right\rangle = 0 \tag{2.49}$$

$$\left\langle \Psi_{ij}^{ab} \left| e^{-\hat{T}} \widehat{H}_N e^{\hat{T}} \right| \Psi_0 \right\rangle = 0 \tag{2.50}$$

$$\left\langle \Psi_{ijk\cdots}^{abc\cdots} \left| e^{-\hat{T}} \widehat{H}_N e^{\hat{T}} \right| \Psi_0 \right\rangle = 0.$$
(2.51)

The obtained energies are identical to those obtained at the full configuration interaction (FCI) level of theory, as all possible excited determinants are included. In other words, the CC wavefunction is a nonlinear reparameterization of the FCI wavefunction, and optimization of the cluster amplitudes yields the FCI wavefunction.<sup>55</sup> However, the interest in CC theory does not stem from solving for all of the amplitudes, after all, FCI already exists. Rather, the CC approach allows for a more natural truncation of excitation amplitudes than that observed from the CI approach.

Utilizing the Baker-Campbell-Hausdorff expansion, the similarity transformed Hamiltonian, Equation (2.48), is simplified to,

$$e^{-\hat{T}}\hat{H}_{N}e^{\hat{T}} = \hat{H}_{N} + \left[\hat{H}_{N},\hat{T}\right] + \frac{1}{2!}\left[\hat{H}_{N},\hat{T}\right]_{2} + \frac{1}{3!}\left[\hat{H}_{N},\hat{T}\right]_{3} + \frac{1}{4!}\left[\hat{H}_{N},\hat{T}\right]_{4}, \qquad (2.52)$$

where,

$$\left[\widehat{H}_{N},\widehat{T}\right]_{n} = \left[\left[\widehat{H}_{N},\widehat{T}\right]_{n-1},\widehat{T}\right], \text{ for } n > 1.$$
(2.53)

The expression terminates after the fifth term since only one- and two-electron terms are present in the normal-ordered Hamiltonian. To conclude, a set of nonlinear equations have been derived from the exponential *ansatz* enabling one to iteratively solve for the cluster amplitudes and their associated contributions to the correlational energy.<sup>55</sup>

#### 2.2.4. Truncating the Cluster Operator

As mentioned in the previous section, interest in coupled cluster theory arises from the fact that truncation of the cluster operator comes about more naturally than that of the CI excitation operator. This is achieved by taking the Taylor series expansion the cluster operator, which, after rearranging the operators by excitation level, yields the following expression,
$$e^{\hat{T}} = 1 + \hat{T}_1 + \frac{\hat{T}_2}{2!} + \dots + \frac{\hat{T}_n}{n!} = 1 + \hat{\phi}_1 + \hat{\phi}_2 + \dots + \hat{\phi}_n, \qquad (2.54)$$

where  $\hat{\phi}_n$  generates all the *n*-electron excitations. Using the fact that the cluster operators commute with one another, the following expressions for  $\hat{\phi}$  in terms of  $\hat{T}$  can be obtained for the first three excitation levels:

$$\hat{\phi}_1 = \hat{T}_1, \tag{2.55}$$

$$\hat{\phi}_2 = \frac{1}{2}\hat{T}_1^2 + \hat{T}_2, \qquad (2.56)$$

$$\hat{\phi}_3 = \frac{1}{6}\hat{T}_1^3 + \hat{T}_1\hat{T}_2 + \hat{T}_3.$$
(2.57)

That is, the first excitation operator generates the single excitations only through the excitation of a single electron. However, for the case of the second excitation operator,  $\hat{T}_2$ , the excitation of two electrons can be achieved through the simultaneous excitation of two electrons,  $\hat{T}_2$ , or the independent excitation of two single electrons,  $\hat{T}_1^2$ . The third excitation operator,  $\hat{T}_3$ , describes the excitation of three electrons, which can be accomplished via the independent excitation of three electrons,  $\hat{T}_1^3$ , independent excitations of one and two electrons,  $\hat{T}_1\hat{T}_2$ , or through the simultaneous excitation of three electrons,  $\hat{T}_3$ . So the electrons of three electrons of one and two electrons,  $\hat{T}_1\hat{T}_2$ , or through the simultaneous excitation of three electrons,  $\hat{T}_3$ .

$$|\Psi_{CC}\rangle = |\Phi_0\rangle + \sum_a^{occ} \sum_r^{virt} c_a^r |\Phi_a^r\rangle + \sum_{a < b}^{occ} \sum_{r < s}^{virt} c_{ab}^{rs} |\Phi_{ab}^{rs}\rangle + \cdots,$$
(2.58)

where  $c_a^r$  are coefficients which represent the cluster amplitudes for the expanded cluster operators. The coefficients for the first three excitations are related to the cluster amplitudes through,

$$c_a^r = t_a^r, \tag{2.59}$$

$$c_{ab}^{rs} = t_{ab}^{rs} + t_a^r \times t_b^s, \tag{2.60}$$

$$c_{abc}^{rst} = t_a^r \times t_b^s \times t_c^t + t_a^r \times t_{bc}^{st}.$$
(2.61)

In the above expressions,  $\times$  denotes the antisymmetric product. The use of the antisymmetric product is required to ensure the antisymmetry principle holds for the exchange of any two occupied or unoccupied spin orbitals. It is of particular interest to notice the expression for the coefficient for triplet excitations, (2.61). That is, the coefficients are the product of single- and double- excitation amplitudes. Hence, contribution from the triples term can be calculated through

the use of only the singles and doubles amplitudes, as opposed to having to explicitly calculate the triples amplitudes.

The most common use of CC theory involves truncation of the cluster operator after the doubles term. This method is referred to as Coupled Cluster Singles and Doubles (CCSD), in which the cluster operator is simply the sum of the two individual excitation operators, which were explicitly shown in Equations (2.39) and (2.41). Solving the CC equations for the singles amplitudes yields,

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$$t_{i}^{a}D_{i}^{a} = f_{ai} + \sum_{e} t_{i}^{e}F_{ae} - \sum_{m} t_{m}^{a}F_{mi} + \sum_{me} t_{im}^{ae}F_{me} - \sum_{nf} t_{n}^{f}\langle na \| if \rangle$$
  
$$-\frac{1}{2}\sum_{mef} t_{im}^{ef}\langle ma \| ef \rangle - \frac{1}{2}\sum_{men} t_{mn}^{ae}\langle nm \| ei \rangle.$$
(2.62)

Equivalently for the doubles amplitudes,

$$t_{ij}^{ab} D_{ij}^{ab} = \langle ab \| ij \rangle + P(ab) \sum_{e} \left[ t_{ij}^{ae} \left( F_{ae} - \frac{1}{2} \sum_{m} t_{m}^{b} F_{me} \right) \right] \\ - P(ij) \sum_{m} \left[ t_{im}^{ab} \left( F_{mj} + \frac{1}{2} \sum_{e} t_{j}^{e} F_{me} \right) \right] + \frac{1}{2} \sum_{mn} \tau_{mn}^{ab} W_{mnij} \\ + \frac{1}{2} \sum_{ef} \tau_{ij}^{ef} W_{abef} \\ + P(ij) P(ab) \sum_{me} \left( t_{im}^{ae} W_{mbej} - t_{i}^{e} t_{m}^{a} \langle mb \| ej \rangle \right) \\ + P(ij) \sum_{e} \left( t_{i}^{e} \langle ab \| ej \rangle \right) - P(ab) \sum_{m} \left( t_{m}^{a} \langle mb \| ij \rangle \right).$$

Where P(ij) is a permutation operator of the form,

$$P(ij)\Omega(x,y) = \Omega(x,y) - \Omega(y,x), \qquad (2.64)$$

with  $\Omega(x, y)$  being an arbitrary function. Additionally, the F intermediates are defined as follows:

$$F_{ae} = (1 - \delta_{ae})f_{ae} - \frac{1}{2}\sum_{m} t_m^a f_{me} + \sum_{mf} t_m^f \langle ma \| fe \rangle - \frac{1}{2}\sum_{mnf} \tilde{\tau}_{mn}^{af} \langle mn \| ef \rangle$$
(2.65)

$$F_{mi} = (1 - \delta_{mi})f_{mi} + \frac{1}{2}\sum_{e} t_i^e f_{me} + \sum_{en} t_n^e \langle mn \| ie \rangle + \frac{1}{2}\sum_{nef} \tilde{\tau}_{in}^{ef} \langle mn \| ef \rangle$$
(2.66)

$$F_{me} = f_{me} + \sum_{nf} t_n^f \langle mn \| ef \rangle.$$
(2.67)

Whereas the *W* intermediates are defined as follows:

$$W_{mnij} = \langle mn \| ij \rangle + P(ij) \sum_{e} t_j^e \langle mn \| ie \rangle + \frac{1}{4} \sum_{ef} \tau_{ij}^{ef} \langle mn \| ef \rangle$$
(2.68)

$$W_{abef} = \langle ab \| ef \rangle - P(ab) \sum_{m} t_{m}^{b} \langle am \| ef \rangle + \frac{1}{4} \sum_{mn} \tau_{mn}^{ab} \langle mn \| ef \rangle$$
(2.69)

$$W_{mbej} = \langle mb \| ej \rangle + \sum_{f} t_{j}^{f} \langle mb \| ef \rangle - \sum_{n} t_{n}^{b} \langle mn \| ej \rangle - \sum_{nf} \left( \frac{1}{2} t_{jn}^{fb} + t_{j}^{f} t_{n}^{b} \right) \langle mn \| ef \rangle.$$

$$(2.70)$$

Note that  $\tau$  and  $\tilde{\tau}$  were used to simplify the expressions, and correspond to the following combinations of excitation amplitudes:

$$\tau_{ij}^{ab} = t_{ij}^{ab} + t_i^a t_j^b - t_j^a t_i^b$$
(2.71)

$$\tilde{t}_{ij}^{ab} = t_{ij}^{ab} + \frac{1}{2} \left( t_i^a t_j^b - t_i^b t_j^a \right).$$
(2.72)

Lastly, *D* is the diagonal elements from the Fock matrix (i.e. the inverse orbital energies), which are defined as follows:

$$D_i^a = F_{ii} - F_{aa}, \tag{2.73}$$

$$D_{ij}^{ab} = F_{ii} + F_{jj} - F_{aa} - F_{bb}.$$
 (2.74)

Similarly, to MP2, the amplitudes are calculated iteratively. In general, the guess for the  $t_i^a$  amplitudes are simply zero, whereas those for the  $t_{ij}^{ab}$  amplitudes are the corresponding MP2 amplitudes. Hence, prior to performing a CCSD calculation one typically calculates the MP2 amplitudes to use as an initial guess. The guess and corrected amplitudes are inserted into the right-hand side of Equations (2.62) and (2.63) yielding the next set of amplitudes.<sup>55</sup>

In general, CCSD calculations can achieve an accuracy of 0.005 Å for bond lengths, and 50 kJ mol<sup>-1</sup> for electronic energies.<sup>55</sup> This is reasonable, however, for applications such as high-resolution spectroscopy, higher accuracies are sometimes required to aid in the assignment of clustered spectra. One of the most well-known methods for achieving said accuracy increase is termed CCSD(T) and is identical to CCSD with the inclusion of triples amplitudes via non-iterative perturbation theory. The CCSD(T) Hamiltonian can be written in a way analogous to that for MP2, and the triples amplitudes are simply calculated using the exact same formula as that for MP4, however, the converged CCSD amplitudes are used instead of the perturbation coefficients. Corrections to the energy arising from the triples contributions are then the fourth and fifth order

terms from the perturbative corrections, describing the coupling between singles and triples. The triples corrections to the energy can simply be added to the CCSD energy,

$$E_{\text{CCSD}(T)} = E_{\text{CCSD}} + E^{(4)} + E^{(5)}.$$
 (2.75)

Where the corrections are given by the following expressions:

$$E^{(4)} = \frac{1}{36} \sum_{ijkabc} t^{abc*}_{ijk} D^{abc}_{ijk} t^{abc}_{ijk}$$
(2.76)

$$E^{(5)} = \frac{1}{4} \sum_{ijkabc} \langle jk \| bc \rangle t_i^{a*} t_{ijk}^{abc}.$$
 (2.77)

Where  $D_{ijk}^{abc}$  are the diagonal elements of the Fock matrix. In a way analogous to Equations (2.62) and (2.63), the triples amplitudes can be obtained via,

$$D_{ijk}^{abc}t_{ijk}^{abc} = P(i|jk)P(a|bc) \left[ \sum_{d} \langle bc \| di \rangle t_{jk}^{ad} - \sum_{l} \langle la \| jk \rangle t_{il}^{bc} \right].$$
(2.78)

Where the permutation operator is defined such that P(i|jk)f(ijk) = f(ijk) - f(jik) - f(kij). The widespread popularity of CCSD(T) can be attributed to the high-level of accuracy that it is capable of achieving, with a reasonable increase in computational cost.<sup>55</sup> Unfortunately, as one includes higher excitation amplitudes, the methods dependence on basis set size increases exponentially. As such, one must employ at least a triple zeta basis set in order for CCSD(T) calculations to be reliable, with larger quadrupole zeta basis sets being preferred. This basis set requirement makes it such that only molecules of up to approximately 30 atoms can be calculated at the CCSD(T) level of theory.<sup>55</sup>

#### 2.3. Quantum Chemistry: Excited State Calculations

As discussed in the section above, quantum chemistry is most commonly applied to calculate the ground state properties of molecules, by solving the electronic Schrödinger equation for the lowest-energy solution of the electronic Hamiltonian operator. Solutions to the higher roots of the operator relate to the electronically excited states, and unfortunately, require the use of substantially more complex algorithms. The electronic wavefunction for molecules in the ground state is typically dominated by a single configuration, and as such, can be accurately represented by a single Slater determinant (Section 2.2.1). Excited states on the other hand, require one to examine the wavefunction to confirm whether it can be treated with a single-reference method, such as those mentioned in the paragraph above, or if they require the use of a multi-

configurational technique. Additionally, one must determine whether the excited state is a bound or dissociative state, which is an entirely different problem in and of itself.

Unlike the previously discussed ground state calculations, calculations for electronically excited states are much more complex, and the results require a careful analysis. Vertical excitation energies, adiabatic excitation energies, geometry optimizations, and vibrational frequencies were performed for  $\alpha$ -alanine. A few different well-known approximations were used to ensure the reproducibility of results, those being the equation of motion coupled cluster (EOM-CC)<sup>61</sup> and symmetry adapted cluster-configuration interaction (SAC-CI)<sup>62</sup> theories. At the time this thesis is being written, only the EOM-CC calculations have finished, and as such, only EOM-CC will be discussed in detail. Additionally, a brief introduction to configuration interaction theory will be included.<sup>63</sup>

# 2.3.1. Configuration Interaction-Singles

The basis of most single-configurational techniques for examining excited states is the configuration interaction-singles (CIS) approach. CIS, just like HF for the ground state, is the computationally and conceptually simplest method available for the calculation of excited state properties.<sup>55</sup> One must first optimize the ground state Slater determinant, Equation (2.9), through the HF procedure. Here we will denote this determinant as,

$$\Phi_0(\mathbf{r}) = |\phi_1(r)\phi_2(r)\cdots\phi_n(r)|, \qquad (2.79)$$

where  $\emptyset_n(r)$  refers to the doubly occupied spatial orbitals. Insertion of this wavefunction into the time-independent HF equation yields the optimized occupied and virtual molecular orbitals (Section 2.2.1). In this section, indices *i*, *j*, *k* refer to occupied orbitals, *a*, *b*, *c* refer to virtual orbitals, and *p*, *q*, *r* refer to general orbitals.

In the CIS method the excited Slater determinants are constructed via replacing occupied orbitals with virtual ones in the ground state Slater determinant. For example, replacing any occupied orbital *i* with any virtual orbital *a*, then the single excited Slater determinant is denoted as  $\Phi_i^a(r)$ . Note that one must only include single excitations. The electronic wavefunction can now be constructed as a linear combination of these excited state determinants along with the ground state wavefunction through the following *ansatz*,

$$\Psi_{\text{CIS}} = \sum_{ia} c_i^a \Phi_i^a(r).$$
(2.80)

Substitution into the time-independent Schrödinger equation with the electronic Hamiltonian operator, followed by projection from the left onto the singly excited determinants,  $\langle \Phi_j^b |$ , gives the following expression:

$$\sum_{ia} \langle \Phi_j^b | \hat{H} | \Phi_i^a \rangle c_i^a = E_{\text{CIS}} \sum_{ia} c_i^a \delta_{ij} \delta_{ab}.$$
 (2.81)

From the above equation, one can easily obtain an expression for the excitation energies,

$$\sum_{ia} \{ (\varepsilon_a - \varepsilon_i) \delta_{ij} \delta_{ab} + \langle ia || jb \rangle \} c_i^a = \omega_{\text{CIS}} \sum_{ia} c_i^a \delta_{ij} \delta_{ab}, \qquad (2.82)$$

which utilizes the relation:

$$\left\langle \Phi_{j}^{b} \middle| \widehat{H} \middle| \Phi_{i}^{a} \right\rangle = (E_{0} + \varepsilon_{a} - \varepsilon_{i}) \delta_{ij} \delta_{ab} + \langle ia || jb \rangle.$$
(2.83)

Recall that  $\varepsilon_a$  and  $\varepsilon_i$  are the orbital energies for the single-electron orbitals  $\phi_a$  and  $\phi_i$ , and  $\langle ia || jb \rangle$  represents the antisymmetrized two-electron integrals (defined in Section 2.2.1). Just as we did for the HF method, converting Equation (2.83) into a matrix eigenvalue equation:

$$\mathbf{AC} = \omega \mathbf{C},\tag{2.84}$$

where **A** is the Hamiltonian matrix projected onto the space of the singly excited determinants,  $\omega$  is the diagonal matrix of excitation energies, and **C** is the matrix of CIS expansion coefficients,  $c_i^a$ . By definition, the matrix elements of the Hamiltonian are given by,

$$\mathbf{A}_{ia,ib} = (\varepsilon_a - \varepsilon_i)\delta_{ii}\delta_{ab} + \langle ia \| jb \rangle.$$
(2.85)

Thus, diagonalization of  $\mathbf{A}$ ,  $(\mathbf{A} - \omega)\mathbf{C} = 0$ , yields the excitation energies. In particular, just as was true for HF, the eigenvalues and eigenvectors from the diagonalization correspond to the excitation energies and expansion coefficients, respectively.<sup>55</sup>

#### 2.3.2. Equation of Motion Coupled Cluster Theory

EOM-CC is a well-known single reference technique that can be applied to the calculation of excited, electron attached, and ionization states. The excited state wave functions,  $\Psi_{EX}$ , are obtained from the ground state wave function,  $\Psi_{GS}$ , through the use of a linear excitation operator,

$$|\Psi_{EX}\rangle = \hat{\mathcal{R}}|\Psi_{GS}\rangle, \qquad (2.86)$$

where  $\hat{\mathcal{R}}$  denotes the total linear excitation operator.<sup>61</sup> For excitation energies,  $\hat{\mathcal{R}}$  is a CI-like particle conserving operator, however, for the ionization and electron attachment cases it is simply

a net annihilation or net creation operator, respectively.<sup>61</sup> However, since we are only concerned with the excitation energies no details regarding the ionization and attachment cases will be discussed. For an excited state, N,  $\hat{\mathcal{R}}_N$  has the form,

$$\widehat{\mathcal{R}}_{N} = \frac{1}{N!^{2}} \sum r_{ijk\cdots}^{abcd\cdots} a^{\dagger} i b^{\dagger} j c^{\dagger} k d^{\dagger} \cdots, \qquad (2.87)$$

where  $a, b, c, d \cdots$  and  $i, j, k \cdots$  denote the unoccupied and occupied orbitals respectively. The total linear excitation operator is simply the sum of the individual operators,

$$\hat{\mathcal{R}} = \sum_{N} \hat{\mathcal{R}}_{N}.$$
(2.88)

Recall that the ground state coupled cluster wavefunction was discussed in detail in Section 2.2.3 of this thesis and can be seen in Equation (2.58). Substituting the ground state coupled cluster wavefunction and Equation (2.86) into the Schrödinger equation yields,

$$\widehat{H}\widehat{\mathcal{R}}e^{\widehat{T}}|\Phi_{0}\rangle = E\widehat{\mathcal{R}}e^{\widehat{T}}|\Phi_{0}\rangle = \underbrace{\left(e^{-\widehat{T}}\widehat{H}e^{\widehat{T}} - E\right)}_{\widehat{H}_{eff}}\widehat{\mathcal{R}}|\Phi_{0}\rangle = 0.$$
(2.89)

The simplification of Equation (2.89) arises from the fact that  $\hat{\mathcal{R}}$  and  $\hat{T}$  must commute.<sup>61</sup> If one denotes the effective Hamiltonian  $\hat{H}_{eff}$  as  $\hat{H}_{eff} = e^{-\hat{T}}\hat{H}e^{\hat{T}} - E$ , then Equation (2.89) presents itself as a typical eigenvalue problem,

$$\widehat{H}_{eff}\widehat{\mathcal{R}}|\Phi_0\rangle = 0. \tag{2.90}$$

EOM-CC is a formally exact method, meaning that the similarity transformation presented above does not change the eigenvalues of the full Hamiltonian.<sup>61</sup> However, just as is true for standard coupled cluster theory, the treatment of all excitations is infeasible, and as such, the operator must be truncated. This is done in a fashion identical to that discussed in Section 2.2.4. Most commonly, single and double excitations are considered. This is known as the EOM-CCSD approximation, which is the equation of motion equivalent to CCSD. Just like CCSD, EOM-CCSD provides an exact treatment of two-electron systems, as no higher order excitations are possible (3 electrons cannot be excited if only 2 electrons exist).

Expressing the effective Hamiltonian in the spin-orbital basis yields,

$$\widehat{H}_{eff} = \sum_{pq} F_{pq} p^{\dagger} q + \frac{1}{4} \sum_{pqrs} W_{pqrs} p^{\dagger} q^{\dagger} sr + \cdots, \qquad (2.91)$$

where F and W are the one- and two-body amplitudes respectively, whose leading terms correspond to the Fock matrix elements and two-electron integrals, with remaining contributions

coming from the appropriate contractions between the Hamiltonian and the  $\hat{T}$  amplitudes that parametrize the ground state wavefunction. Unlike the standard Hamiltonian, the effective Hamiltonian contains three- and higher-body operators. The effective Hamiltonian takes on the following matrix form,

$$\widehat{H}_{eff} = \begin{pmatrix} E_{CC} & \cdots & \cdots \\ 0 & \ddots & \cdots \\ 0 & \vdots & \ddots \end{pmatrix},$$
(2.92)

where the zero terms arise from the condition that  $\hat{T}$  amplitudes obey the coupled cluster equations, as presented in Section 2.2.3. Hence, the ground state coupled cluster solution can be obtained from the root of  $\hat{H}_{eff}$  corresponding to  $\hat{\mathcal{R}} = \hat{\mathcal{R}}_0 = 1$ . Additionally, since  $\hat{H}_{eff}$  is not a Hermitian operator, each root is associated with two eigenvectors,  $\hat{\mathcal{L}}$  and  $\hat{\mathcal{R}}$ , which correspond to the distinct states,

$$\left\langle \widetilde{\Psi} \right| = \left\langle \Phi_0 \right| \hat{\mathcal{L}} e^{\hat{T}}, \tag{2.93}$$

and,

$$|\Psi\rangle = e^T \hat{\mathcal{R}} |\Phi_0\rangle. \tag{2.94}$$

 $\hat{\mathcal{L}}$  is the left eigenvector of  $\hat{H}_{eff}$ , and is a deexcitation operator, which has the same form as the excitation operator  $\hat{\mathcal{R}}$ . That is, the individual and total operator is given by,

$$\hat{\mathcal{L}}_N = \frac{1}{N!^2} \sum r_{ijk\cdots}^{abcd\cdots} a^{\dagger} ib^{\dagger} jc^{\dagger} kd^{\dagger} \cdots, \qquad (2.95)$$

and,

$$\hat{\mathcal{L}} = \sum_{N} \hat{\mathcal{L}}_{N}.$$
(2.96)

Unfortunately, due to the non-Hermitian effective Hamiltonian and intermediate normalization, these states are never Hermitian conjugates. It is of interest to note that excitation energies are the eigenvalues for the excitation operator, and as such, one can neglect the deexcitation terms when calculation the excitation energies. However, for the calculation of all other properties, such as transition densities, the excitation and deexcitation operators must both be evaluated. As a result of the non-Hermitian nature of this eigenvalue problem, we can make the two sets of solutions orthogonal by multiplying them by a unity matrix,

$$\left< \widetilde{\Psi}_i \middle| \Psi_j \right> = c \delta_{ij}, \tag{2.97}$$

which is the EOM-CC normalization condition. It follows to write the energy in its functional form,

$$E = \langle \widetilde{\Psi} | \widehat{H} | \Psi \rangle = \langle \Phi_0 | \widehat{\mathcal{L}} \widehat{H}_{eff} \widehat{\mathcal{R}} | \Phi_0 \rangle.$$
(2.98)

Hellmann-Feynman theorem states that the derivative of the stationary values of a functional with respect to a parameter on which it depends, can be calculated from the explicit dependence, disregarding any and all implicit dependence. Hence, due to the stationary nature of the solutions with respect to variation of the  $\hat{\mathcal{R}}$  and  $\mathcal{L}$  vectors, one can write,

$$\theta = \langle \widetilde{\Psi} | \widehat{\Theta} | \Psi \rangle, \tag{2.99}$$

where  $\widehat{\Theta}$  is an arbitrary linear operator. Using Equation (2.99) as a generalized expectation value, we can calculate properties in the usual way,

$$\theta = \mathrm{Tr}(\rho\Theta), \tag{2.100}$$

where  $\rho$  is the reduced *n*-particle density matrix,

$$\rho_{pq\cdots rs} = \langle p^{\dagger}q^{\dagger}\cdots rs \rangle = \left\langle \Phi_{0} \middle| \hat{\mathcal{L}} \bigl( p^{\dagger}q^{\dagger}\cdots rse^{\hat{T}} \bigr)_{c} \hat{\mathcal{R}} \middle| \Phi_{0} \right\rangle,$$
(2.101)

where the subscript *c* indicates that contractions between the quasiparticle creation and annihilation operators and the *T* amplitudes are restricted to connected diagrams. Elements of the reduced one-particle density matrix suitable for calculating one-electron properties are  $\langle i^{\dagger}j\rangle (\rho_{ij})$ ,  $\langle a^{\dagger}b\rangle (\rho_{ab})$ ,  $\langle i^{\dagger}a\rangle (\rho_{ia})$ , and  $\langle a^{\dagger}i\rangle (\rho_{ai})$ , where the shorthand notation is reported in the parentheses. It is worth noting that the density matrix is only Hermitian when the excitation and deexcitation states are adjoint. Interestingly, since this condition is always satisfied at the exact limit, the non-Hermiticity of the density matrix acts as a measure of the treatment of electron correlation.

## 2.4. Thermodynamics in Molecular Spectroscopy

For flexible molecules with more than one stable configuration, it is useful to compare their relative energies. This is due to the fact that, in the absence of thermal contributions, the relative abundance of each conformer is directly related to their place in the relative energy order. That is, the lowest energy conformer will be the most abundant, with the second lowest being the second most abundant, and so forth.<sup>64</sup> Hence, for experiments performed in the absence of significant thermal sources, such as spectroscopic experiments utilizing seeded supersonic expansions for sample injection, the relative electronic energies greatly simplify spectral assignment by enabling

researchers to better predict which conformers will be observable.<sup>64,65,66</sup> However, for experiments involving temperature variation, such as those presented in this thesis, the absence of temperature dependence in the electronic energy makes it a poor predictor of relative abundance.<sup>67</sup>

For experiments utilizing a variation in temperature, the relative Gibbs free energy,  $\Delta G_T$ , is much more insightful than the relative electronic energy. As a result of the temperaturedependent nature of the Gibbs free energy, the relative abundance of conformers can be calculated at multiple temperatures. This arises due to the fact that the Gibbs free energy takes the vibrational, rotational, translational, and electronic degrees of freedom into account, giving a more accurate prediction of the conformers relative energies.<sup>54</sup> The following subsections highlight the steps required to calculate the relative electronic energies, and relative Gibbs free energies associated with the investigation of  $\alpha$ -serine.

#### **2.4.1. Relative Electronic Energy**

These days, the calculation of a molecules electronic energy is relatively straightforward and can be done with a number of different electronic structure theory techniques (see above Sections). The total electronic energy,  $E_0$ , is obtained from solving the Schrödinger equation through an approximate method, which gives the bottom of the well energy. One can account for the zeropoint vibrational energy (ZPE) effects by simply adding the ZPE to the total electronic energy,

$$E_{ZPE} = E_0 + ZPE. \tag{2.102}$$

The ZPE corrected relative energy can then be calculated by simply subtracting the energy of the most stable conformer. That is,

$$\Delta E_{ZPE,i} = E_{ZPE,i} - E_{ZPE,1}, \qquad (2.103)$$

where  $E_{ZPE,i}$  is the zero-point corrected electronic energy of the *i*<sup>th</sup> conformer, and conformer 1 is the conformer with the lowest electronic energy.

#### 2.4.2. Molecular Partition Functions

The Gibbs free energy at temperature T can be calculated from the following expression,

$$G_T = E_0 + G_{corr}, \tag{2.104}$$

where  $E_0$  is the total electronic energy and  $G_{corr}$  is the thermal corrections to the Gibbs free energy.<sup>68</sup> Thermal corrections to the Gibbs free energy,  $G_{corr}$ , arise directly from the thermal corrections to enthalpy and entropy:

$$G_{corr} = H_{corr} - TS_{corr} \tag{2.105}$$

where  $H_{corr}$  and  $S_{corr}$  are the internal thermal energy contributions to enthalpy and entropy, respectively.<sup>54</sup> Thermal corrections to enthalpy can be calculated with the expression,

$$H_{corr} = \varepsilon_{corr} + k_B T, \qquad (2.106)$$

where  $\varepsilon_{corr}$  is the thermal correction to the internal thermal energy, and  $k_B$  is the Boltzmann constant. The thermal corrections to entropy and internal thermal energy can be directly calculated from the molecular partition functions using the following expressions,

$$\varepsilon_{corr} = \varepsilon_{trans} + \varepsilon_{rot} + \varepsilon_{vib} + \varepsilon_{el}, \qquad (2.107)$$

and,

$$S_{corr} = S_{trans} + S_{rot} + S_{vib} + S_{el}.$$
 (2.108)

Each term in the above equations corresponds to a molecular partition function. These individual contributions can be directly calculated from the partition functions via:

$$\varepsilon_{corr} = Nk_B T^2 \left(\frac{\partial \ln(q)}{\partial T}\right)_V,$$
 (2.109)

and,

$$S_{corr} = R \left( \ln(qe) + T \left( \frac{\partial \ln(q)}{\partial T} \right)_V \right), \tag{2.110}$$

where *R* is the ideal gas constant ( $N_A k_B = R$ ), *N* is the number of moles ( $N = nN_A$ ), *e* is Euler's constant,  $N_A$  is Avogadro's number, and *q* is the product of the individual contributions from each partition function,

$$q = q_{trans} q_{rot} q_{vib} q_{el}.$$
 (2.111)

One must now calculate the individual contributions from each partition function.

Firstly, the translational partition function,  $q_{trans}$ , arises from the movement (translation) of the molecule, and as such, is dependent on the temperature and mass of the molecule:

$$q_{trans} = \left(\frac{2\pi M k_B T}{h^2}\right)^{3/2} V = \underbrace{\left(\frac{2\pi m k_B T}{h^2}\right)^{3/2} \frac{k_B T}{P}}_{Ideal \ Behaviour}.$$
(2.112)

Ideal behavior assumes that the system behaves ideally, that is,  $PV = NRT = (n/N_A)N_Ak_BT$ , hence,  $V = k_BT/P$ . It should be noted that in Equation, *M* is the total mass of the molecule, and *h* is Planck's constant. Taking the partial derivative of the translational partition function with respect to temperature at a constant volume, yields the following expression:

$$\left(\frac{\partial \ln(q_{trans})}{\partial T}\right)_{V} = \frac{3}{2T}.$$
(2.113)

By substituting the above two equations into the conversion relations, Equation (2.109) and (2.110), one obtains expressions for the translational contribution to entropy and internal thermal energy, respectively,

$$S_{trans} = R\left(\ln(q_{trans}e) + T\left(\frac{3}{2T}\right)\right) = R\left(\ln(q_{trans}) + \frac{5}{2}\right),\tag{2.114}$$

and,

$$\varepsilon_{trans} = N_A k_B T^2 \left(\frac{\partial \ln(q_{trans})}{\partial T}\right)_V = \frac{3}{2}RT.$$
 (2.115)

Hence, one can easily obtain the contributions from translation by substituting the known values into the above two expressions.

Similarly, to the translational partition function, the rotational partition function describes the rotational motion of the molecule and is given by the following expression:

$$q_{rot} = \frac{\pi^{1/2}}{\sigma_r} \left( \frac{T^{3/2}}{\left(\Theta_{r,x} \Theta_{r,y} \Theta_{r,z}\right)^{1/2}} \right),$$
 (2.116)

where  $\sigma_r$  is the rotational symmetry number, and  $\Theta_{r,i}$  is the rotational temperature. The rotational temperature can easily be determined from the point group of the molecule. Alternatively, it is equal to the number of times on can rotate the molecule about the molecular axis to obtain an equivalent orientation. Rotational temperature on the other hand, arises from the moment of inertia. That is, the rotational temperature is given by,

$$\Theta_{r,i} = \frac{h^2}{8\pi^2 I_i k_B}, \qquad i = x, y, z \tag{2.117}$$

where  $I_i$  is the moment of inertia with respect to the molecular axis. Notice that the rotational energy levels are given by Hence, for linear polyatomic molecules, the rotational partition function simplifies to  $q_{rot} = \frac{1}{\sigma_r} \left(\frac{T}{\Theta_r}\right)$ , and for single atoms, it further simplifies to  $q_{rot} = 1$ . Continuing on with the general case, the rotational contribution to entropy is obtained by substituting the partition function from (2.116) into (2.110),

$$S_{rot} = R\left(\ln(q_{rot}) + T\left(\frac{\partial\ln(q_{rot})}{\partial T}\right)_V\right) = R\left(\ln(q_{rot}) + \frac{3}{2}\right).$$
(2.118)

Substituting (2.116) into (2.109) yields rotational contribution to internal thermal energy,

$$\varepsilon_{rot} = Nk_B T^2 \left(\frac{\partial \ln(q_{rot})}{\partial T}\right)_V = \frac{3}{2}RT.$$
 (2.119)

Since there are three rotational degrees of freedom, it can be said that the average contribution from each rotational degree of freedom is RT/2.

The concept of the normal mode can about to describe the vibrational motion of a molecule. Hence, it is only natural that the total vibrational partition function is composed of partition functions for each normal mode. Under the harmonic approximation, the total vibrational partition function is the sum of the contributions from each normal mode:

$$q_{vib} = \frac{e^{-hcE_0/k_BT}}{\prod_{i=1}^{n} 1 - \exp(-hcv_i/k_BT)},$$
(2.120)

where  $v_i$  is the fundamental energy associated with mode *i*, and  $E_0$  is the zero-point vibrational energy (ZPE). It is useful to express the partition function in terms of vibrational temperature,  $\Theta_{v,i} = hv_i/k_B$ ,

$$q_{vib} = \frac{e^{-\Theta_{v,i}/2T}}{\prod_{i=1}^{n} 1 - \exp(-\Theta_{v,i}/2T)},$$
(2.121)

where  $\Theta_{v,i}$  is the vibrational temperature of the *i*<sup>th</sup> mode ( $\Theta_{v,i} = hv_i/k_B$ ). In the above two expressions, the zero-point reference for energy is set as the bottom of the well. Interestingly, when calculating the vibrational contribution to entropy and internal thermal energy, one must take the derivative with respect to temperature, and as such, it does not matter if one uses the bottom of the well or zero-point energy as the zero-point. That is, the bottom of the well reference and zero-point reference yield the same contributions to entropy and enthalpy. However, for the sake of completion, when ZPE is taken as the reference zero-point the vibrational partition function has the form,

$$q_{vib} = \prod_{i=1}^{n} \frac{1}{1 - \exp(-\Theta_{v,i}/2T)}.$$
(2.122)

Naturally, it follows that the vibrational components for entropy and internal thermal energy are:

$$S_{vib} = R \left( \ln(q_{vib}) + T \left( \frac{\partial \ln(q_{vib})}{\partial T} \right)_V \right)$$
  
=  $R \sum_i \left( \frac{\Theta_{v,i}/T}{e^{\Theta_{v,i}/T} - 1} - \ln(1 - e^{-\Theta_{v,i}/T}) \right),$  (2.123)

and,

$$\varepsilon_{vib} = Nk_B T^2 \left(\frac{\partial \ln(q_{vib})}{\partial T}\right)_V = R \sum_i \left(\frac{\Theta_{v,i}}{2} + \frac{\Theta_{v,i}}{e^{-\Theta_{v,i}/T} - 1}\right).$$
(2.124)

It is worth noting that one must carefully inspect the low frequency normal modes, which correspond to internal rotations, and ensure that they are treated properly. This is especially important for symmetric top molecules, in which the hindered rotor approximation must be applied. Additionally, anharmonic corrections to the vibrational partition function can be accounted for through the use of simple perturbation theory (SPT).<sup>69</sup> In this case, the harmonic vibrational partition function is still utilized, however, the ZPE and fundamental frequencies are calculated with vibrational perturbation theory (VPT), typically truncated at second order (VPT2).

Within the harmonic approximation, vibrational contribution to entropy results in discrepancies around 1.5 and 0.5 J mol<sup>-1</sup> K<sup>-1</sup> for molecules with and without hindered internal rotations.<sup>70</sup> Accounting for anharmonic corrections reduces these discrepancies to approximately 0.5 and 0.2 J mol<sup>-1</sup> K<sup>-1</sup>, respectively.<sup>70</sup> It is interesting to note that the improvement in accuracy largely results from the anharmonic ZPE, as opposed to the anharmonic corrections to each fundamental transition.

Electronic motion within a molecule is characterized by the electronic partition function,  $q_{el}$ , which is given by,

$$q_{el} = \sum_{i} \omega_{i} e^{\left(\frac{-E_{i}}{k_{B}T}\right)}, \quad i = 0, 1, 2, ...$$
 (2.125)

where  $\omega_i$  and  $E_i$  are the degeneracy and energy of the *i*<sup>th</sup> electronic state. Making the assumption that all excited electronic states have excitation energies much greater than  $k_BT$ , such that they are inaccessible at any temperature, reduces the number of excited states to zero. Additionally, if the ground state energy,  $E_0$ , is set to zero, then the electronic partition function further simplifies to,

$$q_{el} = \omega_0, \tag{2.126}$$

which is equal to one for non-degenerate ground states. This assumption is reasonable for molecules at low temperatures, such as those presented in this thesis. The electronic contribution to entropy can now be determined by substituting (2.126) into (2.110),

$$S_{el} = R\left(\ln(q_{el}) + T\left(\frac{\partial \ln(q_{el})}{\partial T}\right)_V\right) = R\ln(q_{el}) = R\ln(\omega_0).$$
(2.127)

Notice that the above expression is equal to zero for molecules with non-degenerate ground states. A quick inspection of the electronic partition function indicates that there are no temperature dependent terms, and as a result of this, the contribution to internal thermal energy is zero,

$$\varepsilon_{el} = Nk_B T^2 \left(\frac{\partial \ln(q_{el})}{\partial T}\right)_V = 0.$$
 (2.128)

Finally, the thermal corrections to entropy and internal thermal energy are given by the following expressions:

$$S_{corr} = R \left[ \ln(q_{trans} \times q_{rot} \times \omega_0) + \sum_i \left( \frac{\Theta_{\nu,i}/T}{e^{\Theta_{\nu,i}/T} - 1} - \ln(1 - e^{-\Theta_{\nu,i}/T}) \right) + 4 \right], \quad (2.129)$$

and,

$$\varepsilon_{corr} = R \left[ 3T + \sum_{i} \left( \frac{\Theta_{\nu,i}}{2} + \frac{\Theta_{\nu,i}}{e^{-\Theta_{\nu,i}/T} - 1} \right) \right], \tag{2.130}$$

assuming ideal behavior. The relative Gibbs free energy for conformer i at temperature T can now be calculated with the expression,

$$\Delta G_{T,i} = G_{T,i} - G_{T,1}, \tag{2.131}$$

where  $G_{T,i}$  and  $G_{T,1}$  are the Gibbs free energies for molecular conformers *i* and 1 at temperature *T*.

## 2.4.3. Boltzmann Distribution Law

The Boltzmann distribution law states that for a system at temperature T, the probability of a state with energy  $E_i$  is,

$$P(E_i) = \frac{e^{-E_i/k_B T}}{\sum_j e^{-E_j/k_B T}},$$
(2.132)

where *j* is the total number of occupied states. As noted at the start of Section 2.4, we are primarily interested in the Gibbs free energy, and as such, we calculate the Boltzmann distribution using the Gibbs free energy. It is of interest to note that the Boltzmann distribution law says that the population of higher energy states increases with temperature. Therefore, by varying the sublimation temperature, one changes the conformational distribution of the molecule, further simplifying the spectral assignment procedure by enabling the cross-examination of spectra to identify the change in spectral intensity for a given transition with respect to sublimation temperature.<sup>67</sup>

# **3. Results and Discussion**

# 3.1. Conformational Dynamics of $\alpha$ -serine in Solid Parahydrogen Matrices

The physicochemical properties of  $\alpha$ -serine were investigated through the use of solid parahydrogen MI-FTIR spectroscopy. This application of MI-IR spectroscopy for conformational studies is made possible by the fact that the conformational distribution at the sublimation temperature is preserved upon deposition into the matrix.<sup>71</sup> However, in order to accurately predict the conformational distribution at some temperature, one must also know all the barriers to conversion for the molecular species. That is, the barrier for a given conformer to convert into a lower energy conformer through the rotation of a torsion. If the thermal energy of the environment is higher than this barrier, then the conformer will freely convert to the lower energy species, and not be observable. As a rule of thumb, it is said that if the barrier to conversion between two conformers is less than 5 kJ mol<sup>-1</sup>, then the higher energy conformer will tunnel to the lower energy species.<sup>71,72</sup> For highly flexible molecules, such as  $\alpha$ -serine, calculating all possible barriers to conversion would require the consideration of hundreds of saddle-points, up to fifth order. As such, it is not plausible to calculate all of the barriers to conversion. Rather, one crudely estimates the conformational distribution based on the Boltzmann distribution, which is calculated from the Gibb's free energy of the conformers with the understanding that all of the low energy conformers may not be stable enough to be observed. Hence, careful assignment of the experimental spectrum is required.

For flexible molecules, it is expected that the experimental spectrum will contain many conformers, and as such, will be very crowded. In order to accurately assign vibrational bands, the use of highly accurate anharmonic vibrational calculations is required. These calculations enable one to accurately assign the low-intensity features for the most abundant conformers, further increasing confidence in the assignment of lower-abundant conformers, for which only the strongest fundamental transitions will be observed. Another common technique to improve confidence in the assignment is to experimentally shift the conformational ratio correlating observed changes in the relative intensity. This is possible since the intensity of transitions from a given conformer will always change uniformly. One method to shift the conformational ratio involves selective irradiation with a near-infrared laser to induce conformational changes and is generally referred to as a pump-probe experiment.<sup>73</sup> Other methods include annealing the matrix,

*in situ* broad-band or selective UV irradiation, and variation of the sublimation temperature.<sup>74,75,76</sup> The latter method is utilized here, and operates on the principle that the conformational distribution can be calculated from the relative Gibb's free energy, which is temperature dependent. As such, changing the temperature will result in a change in the conformational distribution. In particular, variation of sublimation temperature was used to alter the conformational population of  $\alpha$ -serine conformers.

This section aims to assign the experimental mid-IR spectrum of  $\alpha$ -serine in solid parahydrogen matrices at various sublimation temperatures. The first subsection will be dedicated to a detailed analysis of the spectrum taken with a sublimation temperature of 420 K. Whereas the following subsection will include a comparison of the assigned bands with those observed at 400, 410, and 430 K.

#### **3.2.** Experimental and Computational Parameters for $\alpha$ -serine

The basis of the experimental techniques and computational methods are described in detail in Section 2 of this thesis. Rather, this section details the exact experimental conditions and computational methods employed for the analysis of  $\alpha$ -serine. Analysis of the experimental data can be found in the following subsections. The following experiments were primarily completed by Alethea Lee and Shin Toh during the summer of 2016.

Deposition of the  $\alpha$ -serine sample (L-serine, 99%, and D,L-serine, >98%, Millipore Sigma) was performed with sublimation temperatures of 400, 410, 420, and 430 K (Figure B.1 to Figure B.4). Spectra were registered at 4 K in the 700 – 4800 wavenumber range with a resolution of 0.1 cm<sup>-1</sup> over 1000 scans. Spectral band intensities, widths, and areas of overlapping peaks were obtained through the use of Gaussian and Lorentzian fitting functions. The most intense serine peaks were observed with a sublimation temperature of 420 K, and as such, this spectrum was used for the primary spectral assignment, with all other spectra being used for verification of said assignment. Interestingly, the 430 K spectrum displayed significant spectral features consistent with thermal decomposition. Additionally, the intensity of characteristic serine peaks in the 410 and 430 K deposition spectra are very similar. Unfortunately, due to the complexity of the experimental spectra, the exact concentration of  $\alpha$ -serine in the matrix is unknown for all experiments.

The 15 lowest energy conformers of  $\alpha$ -serine, as depicted below in Figure 3.1, were selected from both, the works of Gronert and O'Hair, and He and Allen.<sup>16,18</sup> Both works were considered when choosing the conformers due to the necessity of considering all low energy configurations. The nomenclature utilized in this thesis follows no logical order, rather, it is based upon the reference works from which the initial structures were obtained. Due to the large number of studies on  $\alpha$ -serine, a conversion table for the nomenclature presented in studies closely related to this work can be found in the appendix. The optimized geometry and anharmonic vibrational frequencies were calculated for all 15 conformers at the DFT and MP2 levels of theory, with the Gaussian 16 suite of programs.<sup>77</sup> For the sake of consistency, all calculations are identical to those completed for the D-enantiomer. Additionally, the frozen core approximation was utilized in all calculations.

The Becke 3-parameter Lee-Yang-Parr hybrid functional  $(B3LYP)^{36,37}$  with the inclusion of Grimme's empirical atom-pairwise dispersion corrections, D3,<sup>78</sup> and Becke-Johnson damping, BJ,<sup>79</sup> was employed for all DFT calculations. Note that the above method is commonly denoted as B3LYP-D3BJ. All DFT calculations were performed with Alhrichs triple zeta property optimized split-valence basis set with additional polarization and diffuse functions, def2-TZVPD.<sup>80,81</sup> Due to the floppy nature of  $\alpha$ -serine, a pruned integration grid consisting of 175,974 for hydrogen and 250,974 points for carbon, nitrogen, and oxygen was used.

MP2 geometry optimizations were performed with Dunning's augmented correlation consistent triple zeta split-valence basis set with additional polarization and diffuse functions, augcc-pVTZ.<sup>82</sup> Whereas the MP2 anharmonic frequencies were calculated with the slightly smaller correlation consistent triple zeta split-valence basis set with additional polarization functions, ccpVTZ, which was also introduced by Dunning.<sup>82</sup> It should be noted that the anharmonic frequencies were calculated using geometries optimized with the cc-pVTZ basis set. The smaller basis set was utilized due to the exponential scaling associated with the MP2 method. That is, calculation of the MP2 gradient scales as  $O^2N^3$ , where O and N are the number of occupied and total basis functions respectively. However, the analysis of noncovalent interactions within  $\alpha$ -serine requires the use of diffuse basis functions, which is why the geometries were optimized with the larger aug-cc-pVTZ basis set.

The Berny algorithm developed by Bernhard Schlegel,<sup>83</sup> was used for all DFT and MP2 geometry optimizations. Depurturbed second order vibrational perturbation theory (DVPT2) was utilized for the numerical differential of analytical second derivatives at 72 nuclear displacements (two displacements per normal mode).<sup>84</sup> Additionally, anharmonic vibrational-rotational couplings, and anharmonic IR intensities were calculated within the DVPT2 framework.<sup>85,86,87</sup> Convergence thresholds were set to  $3.7074 \times 10^{-8}$  for the gradient and Hessian,  $3.7074 \times 10^{-5}$ for the cubic and quartic force fields,  $1.0 \times 10^{-3}$  for Coriolis coupling, and  $1.0 \times 10^{-4}$ Å<sup>2</sup> for the inertia. Note the higher convergence requirements for the gradient and Hessian compared to the cubic and quartic force fields. The cubic and quartic force fields are calculated via the numerical differentiation of the Hessian. As such, since the gradient and hessian are analytically calculated, it is optimal to set tighter convergence thresholds to minimize errors observed as a result of said numerical differentiation. Coriolis coupling and inertia refer to the calculation of vibrationalrotational coupling terms. The maximum frequency for 1-2 Fermi resonances, 1-1, and 2-2 Darling-Dennison resonances were set to 200 cm<sup>-1</sup> and 100 cm<sup>-1</sup>, respectively. A maximum tolerance between VPT2 and variational results of 1 cm<sup>-1</sup> was allowed. A minimum value of 1 cm<sup>-1</sup> for off-diagonal 1-1 Darling-Dennison terms was utilized, whereas the minimum for 2-2 Darling-Dennison terms was 10 cm<sup>-1</sup>.

Accurate energies were calculated with the CCSD(T)-F12<sup>88</sup> explicitly correlated coupledcluster (CC) technique available within the ORCA 4 suite of programs.<sup>89,90</sup> These calculations utilized the explicitly correlated cc-pVTZ-F12 basis set,<sup>91</sup> along with the complementary auxiliary basis set (CABS), cc-pVTZ-F12/CABS,<sup>92</sup> and auxiliary cc-pVQZ/C basis set.<sup>93</sup> It should be noted that the resolution of identity (RI) approximation, also known as density fitting, was implemented for the integral transformation during the explicitly correlated portion of the calculation, which drastically reduces computational time.<sup>94</sup> These energies were calculated using geometries optimized at the MP2/aug-cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory, which were discussed above.

Relative stability of the  $\alpha$ -serine conformers was assessed within the quantum theory of atoms-in-molecules (QTAIM)<sup>95</sup> and non-covalent interaction (NCI)<sup>96</sup> frameworks. The MultiWFN<sup>97</sup> suite of programs was employed for the extraction of wavefunctions from the gaussian formatted checkpoint files, and the detection of QTAIM critical points. Reduced density

gradient (RDG) and sign $(\lambda_2)\rho$  cubic files required for the NCI analysis were generated with cubegen, a gaussian 16 utility program. Chimera<sup>98</sup> and ChimeraX<sup>99,100</sup> were utilized for molecular visualization, including the QTAIM critical points, NCI molecular overlays, and the standalone molecules. Scatter plots of the RDG and sign $(\lambda_2)\rho$  cubic functions were created with Igor Pro 8, a suite of programs for graphic and data analysis. A brief overview of NCI theory can be found in Section 3.2.1 of this thesis.

The vibrational potential energy distribution (PED) was calculated for each normal mode through the use of the VEDA 4 program.<sup>101,102</sup> In short, the PED represents the normal mode coordinate as a superposition of local mode coordinates, enabling one to determine the precise energetic contributions to the vibration. Thereby allowing for one to determine which vibrational frequencies will be affected by the presence of noncovalent interactions. This analysis is similar to simply looking at the internal coordinates for a given normal mode. However, using only the internal coordinates often leads to misinterpretation of the normal mode. That is, light atoms, such as hydrogen, may show significant movement for a given normal mode while contributing very little to the change in energy observed during the vibration.

It is worth mentioning that, while not presented in this thesis, geometry optimizations and anharmonic frequency calculations for the conformers of  $\alpha$ -serine at the CCSD(T)/cc-pVQZ level of theory are currently in progress. Briefly, these calculations are being performed with the CFOUR 2.1 suite of programs,<sup>103,104</sup> and utilize analytical gradients, and second derivatives as implemented within CFOUR.<sup>105,106,107,108</sup> At the time of writing, these calculations have not yet finished, and only slight modifications to the experimental assignment are expected upon their completion.



Figure 3.1 Three-dimensional molecular structures of the 15 lowest energy conformers of  $\alpha$ -serine.

# 3.2.1. Noncovalent Interactions in $\alpha$ -serine

In this section the role of noncovalent interactions in the conformational distribution of  $\alpha$ -serine will be discussed in detail. The relative ZPE corrected, and Gibb's free energies at 420 K were

calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory. All calculations were carried out as discussed in Section 3.2. Anharmonic corrections to the vibrational partition function were calculated through the use of SPT, with the three lowest vibrational modes being treated under the hindered rotor approximation. Previous studies have shown that the relative energy of conformers 4, 11, 13, and 14 show significant reductions when calculated with MP2 compared to those calculated with HF.<sup>18</sup> This indicates that accounting for an adequate amount of electron correlation is extremely important, and as such, single point energies were calculated with CCSD(T)-F12, which, as discussed in the previous section, produces electronic energies near the CBS limit. The results of these calculations are summarized below in Table 3.1, whereas the relative Gibb's free energies at other sublimation temperatures can be found in Table 3.4.

Table 3.1. Tabulation of the relative ZPE-corrected electronic energies, and relative Gibbs free energies (420 K) for the 15 lowest energy  $\alpha$ -serine conformers.

а	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
$\Delta E_{\text{DFT}}$	0.00	-0.90	1.84	1.35	7.07	5.81	4.75	7.06	6.39	7.27	7.15	10.43	11.16	15.04	6.91
$\Delta E_{\text{MP2}}$	0.00	-0.96	1.81	1.48	7.01	6.01	4.78	6.96	6.45	7.32	7.31	10.38	11.37	15.15	7.01
B <sub>E,MP2</sub>	20.4	26.8	12.1	13.3	2.7	3.6	5.2	2.8	3.2	2.5	2.5	1.0	0.8	0.3	2.7
$\Delta G_{\text{DFT}}$	0.00	1.09	5.52	2.88	5.65	7.45	6.00	7.53	8.54	7.30	4.88	8.94	9.75	14.24	5.99
$\Delta G_{MP2}$	0.00	1.46	5.34	3.24	5.77	7.93	6.09	7.47	8.77	6.70	6.59	8.59	10.27	13.98	6.33
B <sub>G.MP2</sub>	28.1	18.5	6.1	11.1	5.4	2.9	4.9	3.3	2.3	4.1	4.3	2.4	1.5	0.5	4.6

<sup>a</sup> Anharmonic thermochemical corrections were calculated as described in the main text with MP2 and B3LYP-D3BJ as denoted by the subscript MP2 and DFT. Electronic energies were calculated at the CCSD(T)-F12/cc-pVTZ-F12 level of theory. All energies are reported in kJ mol<sup>-1</sup>. The Boltzmann percentages are reported as  $B_{E,MP2}$  and  $B_{G,MP2}$  for the electronic energies and Gibb's free energies, respectively, all calculated with MP2 values.

As seen in Table 3.1, there is a large difference between the relative electronic energies and Gibb's free energies at 420 K, indicating that thermal effects play a substantial role in the conformational distribution. In order to fully understand the thermal effects, we must first understand the stabilizing and destabilizing forces present within the molecule. The geometrical structure of each conformer is largely determined by the presence and absence of NCIs. Namely, these interactions are hydrogen bonding (HB), steric repulsion, and hyperconjugation. The previously mentioned importance of electron correlation for the accurate calculation of electronic energies confirms that noncovalent interactions play a large role in  $\alpha$ -serine, since significant dependence on electron correlation for the electronic energy has been linked to the presence of NCIs.<sup>109</sup> To gain an understanding into the nature of said noncovalent interactions, they will be probed through the QTAIM<sup>95</sup> and NCI<sup>96</sup> frameworks. Additionally, it is important to mention that these interactions have an effect on vibrational frequencies as the presence of stabilizing or destabilizing interactions results in a blue or red shift of the observed vibrational frequency, respectively, where the magnitude of the shift is dependent on the strength of the interaction. Hence, understanding these interactions will greatly simplify the spectral assignment.

A brief description is included below for the analysis of noncovalent interactions through the NCI framework, as presented by Johnson *et al.* in 2010.<sup>96</sup> It is well known that all chemical properties can be calculated from the quantum-mechanical electron density, denoted as  $\rho$ . Additionally, the reduced density gradient (RDG) is determined from the gradient and first derivative of the electron density,

RDG = 
$$\frac{|\nabla \rho|}{2(3\pi^2)^{1/3}\rho^{4/3}}$$
 (3.1)

RDG is a dimensionless quantity that describes deviations from a homogenous electron distribution. Hence, in the presence of a noncovalent interaction the RDG will approach zero, becoming equal to zero at the exact point of the interaction. In 2010, Johnson *et al.* discovered that the presence of noncovalent interactions is characterized by regions with low density and low reduced gradient.<sup>96</sup> Unfortunately, these regions characterize all noncovalent interactions, regardless of whether they are stabilizing or destabilizing. However, the sign of the Laplacian of the density,  $\nabla^2 \rho$ , is commonly used to distinguish between different types of weak interactions.<sup>96,110</sup> The Laplacian is commonly expressed a sum of individual contributions along the three principal axes of maximal variation,

$$\nabla^2 \rho = \lambda_1 + \lambda_2 + \lambda_3. \tag{3.2}$$

Local maxima regions of the electron density are characterized by negative values for all three eigenvalues. It has been shown that, for noncovalent interactions, the sign of the second eigenvalue,  $\lambda_2$ , will be negative. However, in the case of steric crowding, the sign of  $\lambda_2$  will be positive. Hence, the sign of the second eigenvalue of the Laplacian can be used to distinguish between regions of stabilizing and destabilizing intramolecular interactions. Additionally, the magnitude of the sign of  $\lambda_2$  can be used to characterize the strength of the interaction.<sup>96,110</sup> This procedure was carried out to analyze the noncovalent interactions for 15 low energy conformers of  $\alpha$ -serine, the results of which are presented in Figure 3.2.

As seen in Figure 3.2, each conformer of  $\alpha$ -serine has at least two intramolecular interactions, with most conformers having three or four. NCI indicates that most of these interactions are weak and stabilizing, which, due to the small size of  $\alpha$ -serine, is surprising. The most stable conformer at 420 K, conformer 1, appears to form the weakest intramolecular interactions. On the other hand, conformer 2, which is the second most stable at 420 K and the most stable when only considering the ZPE corrected electronic energies, appears to form the strongest intramolecular interactions. Hence, there is a clear temperature dependence for the steric hinderance observed in the conformers of  $\alpha$ -serine. In other words, in the absence of any thermal contributions, the additional stabilization provided by the noncovalent interactions in conformer 2 make it the lowest energy conformer. However, upon increasing the temperature, the steric effects quickly overcome the stabilization provided by the additional noncovalent interactions, resulting in conformer 1 becoming the lowest energy conformer. However, these results could simply be due to the approximations made within the NCI analysis. As such, it is only fitting that the QTAIM and NCI results be explored together.



Figure 3.2 NCI analysis for the conformers of  $\alpha$ -serine. The colour bar on the right denotes whether the interaction is attractive, repulsive, or weak, denoted by red, blue, green respectively.

Briefly, within the QTAIM framework molecules are divided into atomic basins that are partitioned with respect to critical points in the electron density. A critical point is defined as the

point in which the gradient norm of electron density is zero. There are four types of critical points, which are classified according to the sign of the eigenvalues in the electron density Hessian matrix. These are termed, Nuclear, Bond, Ring, and Cage critical points. As expected, nuclear critical points occur at the center of nuclei, and as described above, all three eigenvalues are negative (local maxima). Bond critical points occur in between attractive atom pairs and correspond to regions with two negative eigenvalues. Ring and cage critical points occur in regions with one and no negative eigenvalues respectively. Notice that bond critical points don't distinguish between noncovalent and covalent interactions. Additionally, QTAIM typically only observes strong intramolecular interactions. Due to the shortcomings of QTAIM, it is advantageous to use it in conjunction with NCI. Of particular interest to this thesis are the bond critical points (BCPs) and ring critical points (RCPs).

From the QTAIM analysis, Figure 3.3, it is clear that most of the interactions observed with NCI are weak as most conformers display only one or two critical points, not include the nuclear or bond critical points corresponding to covalent bonds. Conformers 2, 3, 6, 7, 8, 9, 10, and 12 all contain at least one ring critical point. Based on the NCI analysis, conformers 10 and 12 form the weakest intramolecular interactions of the conformers containing a ring critical point. This is important as the relative energies of conformers 2, 3, 6, 7, 8, and 9 increase when accounting for thermal contributions, whereas those from 10 and 12 slightly decrease. Further supporting the finding that the relative stability of  $\alpha$ -serine conformers is largely dependent on temperature. This is the basis for varying the sublimation temperature, as a slight variation in temperature yields significant changes to the conformation distribution, with a large reduction predicted to be observed for conformers exhibiting substantial intramolecular hydrogen bonding. In addition to the conformers mentioned above, conformer 4 also increases in relative energy upon an increase in temperature. Even though conformer 4 lacks the presence of a ring critical point, NCI shows the presence of three noncovalent interactions with relatively large isosurfaces. As such, the increase in relative energy upon increasing temperature can be attributed to steric hinderances results from the size of the noncovalent interactions present in conformer 4.



Figure 3.3 Projection of QTAIM critical points onto  $\alpha$ -serine. Nuclear critical points are purple, ring critical points are blue, and bond critical points are yellow.

In total, there are sixteen distinct intramolecular interactions that can occur within  $\alpha$ -serine. As such any discussion about the noncovalent interactions will become complicated rather quickly. Prior to any additional discussion about the QTAIM and NCI results, it is useful to partition the conformers into groups based on the noncovalent interactions they display. The groupings are reported below in Table 3.2, in which they are partitioned based upon the "donor" and "acceptor" functional groups for each intramolecular interaction. This will be revisited during the spectral assignment; however, it is worthwhile to introduce it now. The table simply serves to demonstrate the number of noncovalent interactions present in each conformer.

Labol	Conformarda	Conformers <sup>a</sup> Donor		Accepto	Acceptor Group		
Laber	Comorners	Functional	Atom <sup>b</sup>	Functional	Atom <sup>b</sup>		
А	1, 4, 5	Hydroxyl	$H_2C - OH$	Amine	$XC - NH_2$		
В	2, 3, 7, 10	Hydroxyl	$H_2C - OH$	Carboxyl	(HO)C = 0		
С	11, 12	Hydroxyl	$H_2C - OH$	Carboxyl	(H0)C = 0		
D	6, 8, 9, 13, 14, 15	Hydroxyl	$H_2C - OH$	No Inte	eraction		
E	2, 6, 7, 8, 9, 11, 13, 14, 15	Amine	$XC - NH_2$	Hydroxyl	$H_2C - OH$		
F	5, 7, 10, 13	Amine	$XC - NH_2$	Carboxyl	(H0)C = 0		
G	1, 4, 11, 12, 14, 15	Amine	$XC - NH_2$	Carboxyl	(HO)C = <b>O</b>		
	-	Amine	$XC - NH_2$	No Inte	eraction		
	-	Carboxyl	(H0)C = 0	Hydroxyl	$H_2C - OH$		
	-	Carboxyl	(H0)C = 0	Carboxyl	(HO)C = <b>O</b>		
Н	2, 3, 6, 8, 9	Carboxyl	(H0)C = 0	Amine	$XC - NH_2$		
Ι	1	Carboxyl	$(\mathbf{H}0)\mathbf{C}=0$	No Inte	eraction		
J	11	Methyl	XC - H	Hydroxyl	$H_2C - OH$		
Κ	1, 4, 14, 15	Methyl	XC - H	Carboxyl	(H0)C = 0		
L	2, 8, 13	Methyl	XC - H	Carboxyl	(HO)C = <b>O</b>		
	-	Methyl	XC - H	Amine	$XC - NH_2$		

Table 3.2 Summary of noncovalent interactions present in each of the 15 lowest energy conformers.

<sup>a</sup> Empty rows in the conformer column represent that none of the conformers of interest undergo this type of intramolecular interaction. However, the rows were left in for the sake of completion. <sup>b</sup> The bolded atom in the Atom columns represents the primary atom involved in the noncovalent interaction, may it be as the donor or the acceptor. For the carboxyl functional group, (HO) denotes the hydroxyl component, while C = O denotes the carbonyl component.

# 3.2.2. *α*-serine in Solid Parahydrogen Matrices

In order to reproducibly examine the vibrational frequencies in terms of the noncovalent interactions, the total energy distribution for each normal mode was calculated. The internal coordinates,  $S_i$ , are defined in Table B.2 of Appendix B. To make an accurate comparison of the results with those of previous studies, Table B.3 in Appendix B converts all of the internal

coordinates used for the analysis of this thesis to those presented by He and Allen.<sup>18</sup> Additionally, the theoretical vibrational, intensities, and total energy distributions (TED) for all conformers can be found in Table B.4 to Table B.11 of Appendix B. Note that the TED for the vibrational modes calculated at the DFT and MP2 levels of theory are well within the margin of error of the analysis, and as such, only the TED calculated from the MP2 frequencies are presented. A comparison of the vibrational energy distribution for each normal mode across all conformers enables one to ascertain how the vibrational modes change character, thereby providing further insight into the relative stabilities. In addition to the total energy distribution, the internal modes were utilized to assign normal modes.

Based on the relative Gibb's free energies at 420 K, Table 3.1, it is expected that conformers 1, 2, and 4 will be the most abundant species in the spectrum. This is due to the fact they are 2 kJ mol<sup>-1</sup> lower in energy than the next lowest energy conformer, which, according to the Boltzmann distribution, indicates that they should account for 28.1, 18.5, and 11.1 % of the distribution, respectively. Additionally, conformers 3, 5, 6, 7, and 10 have been experimentally observed in argon matrices, and as such, we expect to observe their stronger features. Notice that conformer 6 has a Boltzmann percentage of 2.9 %, whereas that for conformers 8 and 15 are 3.3 and 4.6 % respectively. This is the first experiment to consider conformer 15 and based on the Boltzmann percentages it is reasonable to say that it should be present in measurable quantities. Conformer 8 has been identified in one previous study,<sup>20,21</sup> but more recent studies were unable to observe it.<sup>23</sup> However, based on the Boltzmann distribution, we predict that it should be present in observable amounts. Experimental observation of conformers 9, 11, 12, 13, and 14 is not expected, but they are included in the analysis for the sake of completion. That being said, conformer 11 has the exact same Boltzmann percentage as conformer 10, however,

As a result of the conformational flexibility of  $\alpha$ -serine, the experimental spectrum has many overlapping bands and is very crowded. However, the calculated frequencies indicates that vibrational modes in the 700 – 1000 cm<sup>-1</sup> region should be sufficiently spaced out enabling an initial identification of the conformers present. There are a few different vibrational modes present in this region, namely, NH<sub>2</sub> wagging,  $\omega$ (NH<sub>2</sub>), C – O stretching,  $\nu$ (C – O)<sub>OH</sub> and  $\nu$ (CO)<sub>COOH</sub>, C – N stretching,  $\nu$ (CN), and hydroxyl torsions,  $\tau$ (OH)<sub>OH</sub> and  $\tau$ (OH)<sub>COOH</sub>. Based on the theoretical calculations,  $\omega(NH_2)$  and  $\tau(OH)$  modes are the dominant modes in the spectrum located below 1000 cm<sup>-1</sup>. Note that the  $\nu(C - O)$  modes do appear above 1000 cm<sup>-1</sup> as well.

Unfortunately, the largest peak in the spectrum below  $1000 \text{ cm}^{-1}$  corresponds to ammonia, NH<sub>3</sub>, and can be seen at 968.1 cm<sup>-1</sup>. NH<sub>3</sub> is a well-known thermal product of  $\alpha$  amino acids, which is clearly evident with the peaks growing intensity with an increase in sublimation temperature. Additional NH<sub>3</sub> bands located in the experimental spectrum are 976.9, 986.7, 1608.3, 1608.4, 1641.6, 1641.8, and 1655.67 cm<sup>-1</sup>, all of which have been reported in previous studies.<sup>111,112</sup> A complete list of known NH<sub>3</sub> bands can be found in the corresponding references, and additional impurities present in the experimental spectra are discussed at the end of this subsection. As seen in Figure 3.4F, these bands are relatively sharp, and as such, have little effect on the spectral assignment.



Figure 3.4 Zoomed in sections of the 700 – 1000 cm<sup>-1</sup> regions of the experimental  $\alpha$ -serine spectrum in solid parahydrogen. The T<sub>Sub</sub> = 430 K spectrum has been artificially situated above the other spectra in C, D, and E such that the larger amounts of noise do not interfere with observing other spectral features. Additionally, the T<sub>Sub</sub> = 430 K spectrum was not included in A and B due to an overwhelming amount of noise.

The  $\nu(C - 0)_{OH}$  and  $\nu(C - 0)_{COOH}$  stretching modes are located with the 950 – 1250 cm<sup>-1</sup> region of the experimental spectrum. Compared to other normal modes, these modes

are spread out over a relatively large range which is due to the intramolecular interactions present in the conformers. In general, the  $\nu(C-0)_{OH}$  mode is located in the 950 - 1075 cm<sup>-1</sup> region, and the bands are more intense than those observed for the  $\nu(C - O)_{COOH}$  modes, which are located in the 1150 - 1250 cm<sup>-1</sup> region. This region of the spectrum also contains bands corresponding to  $\nu(C_4 - N)$  stretching modes, along with  $\delta(OH)_{OH}$  and  $\delta(OH)_{COOH}$  bending modes. All of these modes, with the exception of  $\nu(C_4 - N)$ , are dependent on the noncovalent interactions present in the conformer. Bands assigned to the  $\nu(C - 0)_{OH}$  mode were assigned to conformers 1, 2, 3, 4, 5, 6, 8, and 15. Conformers 3 and 8 were assigned to the same band, appearing at 1044.2 cm<sup>-1</sup>, which was done on the basis of intensity, and the broadness of the band. That is, this band has a FWHM of 16.3 cm<sup>-1</sup>, which is substantially broader than the approximately 2 cm<sup>-1</sup> observed for all other conformers. Additionally, bands associated with conformers 7 and 10 were not detected, which is due to the low intensity of these transitions. The strongest band in this region is located at 1108.7 cm<sup>-1</sup> and has been assigned to conformer 1 on the basis of its intensity, and its agreement with the calculated values. A weaker band on the shoulder of this peak is located at 1112.2 cm<sup>-1</sup>, and has been assigned to conformer 4 on the basis of its predicted wavenumber and intensity. That is, it is predicted that this transition will be much weaker for conformer 4 than conformer 1, and this transition is, not only on the shoulder of the transition for conformer 1, but also about one third the intensity, which is within reasonable agreement with the calculated values. As mentioned above, the  $\nu(C-0)_{COOH}$  modes are located in the 1150 - 1250 cm<sup>-1</sup> region of the experimental spectrum. Due to the lower intensity of this transition, only conformers 1, 4, and 5 were detected. Interestingly, the intensity of this transition is strongly dependent on the noncovalent interactions present in the conformer, indicating that the C - O bond is weaker in these conformers.

A quick inspection of the experimental spectrum, Figure 3.5, one will see that the strongest band is located at 1772.2 cm<sup>-1</sup>, which is characteristic of the carbonyl stretching mode,  $v_{C=0}$ . Comparison with the theoretical spectra indeed confirms this. A closer look shows five distinct bands located at 1755.5, 1772.7, 1777.9, 1782.3, and 1790.3 cm<sup>-1</sup>. The band at 1755.5 cm<sup>-1</sup> has been assigned to both conformers 7 and 10. Based on the theoretical frequencies and Gibb's free energies, along with the experimental intensity of the band, it is clear that this band belongs to conformers 7 and 10. That is, no other conformers absorb around 1755.5 cm<sup>-1</sup>, and the intensity of the band is too high to belong to either one of them, however, it matches up with their combined

intensities. Whereas the band at  $1772.7 \text{ cm}^{-1}$  has been assigned to conformers 1 and 5. Based on the shape of the band, it is clear that there are overlapping bands, however, due to the large number of bands in the region skewing the baseline, this particular overlap could not be fit. As such, the  $1772.7 \text{ cm}^{-1}$  band has been assigned to conformer 1, with it being noted that the conformer 5 band is overlapping but was not resolved. Likewise, the band at  $1777.9 \text{ cm}^{-1}$  has been assigned to conformers 3 and 4, with conformer 4 being the larger contributor. Unlike the other bands, the bands at  $1782.3 \text{ and } 1790.3 \text{ cm}^{-1}$  were assigned to conformers 6 and 2. These bands are much sharper than the others mentioned, and do not contain any overlap, hence, their intensities are much lower. These assignments not only agree with previous experiments,<sup>23</sup> but also with the predicted frequencies.



Figure 3.5 Zoomed in sections of the amine (N-H), A, and carbonyl (C=O), B, stretching regions for  $\alpha$ -serine in solid parahydrogen. The T<sub>Sub</sub> = 430 K spectrum has been artificially situated above the other spectra in A such that the larger amounts of noise do not interfere with observing other spectral features.

The NH<sub>2</sub> symmetric stretch,  $\nu(NH_2)_{sym}$ , and asymmetric stretch,  $\nu(NH_2)_{asym}$ , modes of vibration can be seen above in Figure 3.5. It is worth noting that this region is situated in-between two sections of hydroxyl stretching bands, however, bands corresponding to  $\nu(NH_2)$  modes are easily distinguished from those corresponding to  $\nu(OH)$ , as are typically finer (i.e., smaller FWHM) and are much lower in intensity. Due to the decreased intensity of these bands, it is

expected that they will only be observed for the conformers present in fairly large amounts. In general,  $\nu(NH_2)_{sym}$  bands are slightly red shifted compared to  $\nu(NH_2)_{asym}$  bands. As a result of the low intensity and increased noise present in this region, only bands for conformers 1, 2, 3, 4, and 6 were identified.

The methyl stretching,  $\nu(C_4H)$ ,  $\nu(CH_2)_{sym}$ , and  $\nu(CH_2)_{asym}$ , region of the experimental spectrum spans the 2800 – 3000 cm<sup>-1</sup> range, as seen in Figure 3.6. This region is particularly difficult to assign for highly flexible hydrocarbons as a result of the large number of overlapping weak transitions. For instance, based on the predicted frequencies, there should be 37 vibrational bands, most of which are strong enough to be experimentally observed. Due to the high density of transitions, it is highly unlikely than any single band arises from one conformer, but is rather comes from multiple, making any definitive assignment in this region tremendously difficult. As a result of these difficulties, only one other group attempted to assign this portion of the experimental spectrum,<sup>21</sup> and their results are within reasonable agreement to those shown here. Bands from every conformer were assigned in this region, however, due to the large amount of overlap, these assignments should be viewed as tentative.



Figure 3.6 Zoomed in sections of the methyl stretching regions for  $\alpha$ -serine in solid parahydrogen. The T<sub>Sub</sub> = 430 K spectrum has been artificially situated above the other spectra in A such that the larger amounts of noise do not interfere with observing other spectral features.

 $\alpha$ -serine has two distinct O-H stretching vibrational modes from the hydroxyl and carboxyl functional groups. Both the hydroxyl stretching,  $\nu(OH)_{OH}$ , and carboxyl stretching,  $\nu(OH)_{COOH}$ , bands have been identified for conformers 1, 2, 3, 4, 5, 6, 7, 8, 10, and 15. That is, they were identified for all present conformers, and can be seen below in Figure 3.7. Interestingly, the  $\nu(OH)_{OH}$  band corresponds to the first normal mode for every conformer, with the exception of conformers 1, 4, and 5, for which, the  $\nu(OH)_{COOH}$  band is the first normal mode. Unfortunately, the  $\nu(OH)_{OH}$  band for conformer 1, based on the predicted frequencies and previous experiments in argon, occurs at approximately 3542.0 cm<sup>-1</sup>, which is the exact located of waters  $\nu(OH)$ stretching band in parahydrogen. Additionally, the water bands located at 1631.6  $\text{cm}^{-1}$  are too intense to be accurately measured, hence, assignment of the conformer 1 band cannot be done indirectly based on whether or not the band at 3542.0 cm<sup>-1</sup> is more intense than one would expect. The  $\nu(OH)_{OH}$  band is located just below that for conformer 1, and as such, there is a chance that the intensity has been artificially increased as a result. In addition, the  $\nu(OH)_{OH}$  bands for conformers 3 and 5 were previously identified at 3516.9 and 3518.6 cm<sup>-1</sup> respectively, in argon. Here, the presence of a single broad band was located at 3512.6 cm<sup>-1</sup>, and was tentatively assigned to both conformers 3 and 5 based on integration of the band,  $A_{nH_2}$ .

The conformers can be partitioned into two distinct groups based on the  $v(OH)_{COOH}$  mode. Firstly, the  $v(OH)_{COOH}$  mode is the first normal mode for conformers 1, 4, and 5, which is located around 3550 cm<sup>-1</sup>. All of these conformers exhibit a free carboxyl hydrogen, with the oxygen lone pair being a hydrogen bond acceptor from either an amine or alkyl hydrogen. Secondly, the  $v(OH)_{COOH}$  mode is the fourth normal mode for conformers 2, 3, 6, and 8, which is located in the 3200 cm<sup>-1</sup> region. The carboxyl hydrogen in these conformers sufficiently interacting with the amine lone pair such that not only a critical point is found between the two, but also the presence of a ring critical point is detected. Thereby stabilizing the stretching motion and explaining the observed red shift. Lastly, the  $v(OH)_{COOH}$  mode is the second normal mode for conformers 7, 10, and 15, also being located in the 3550 cm<sup>-1</sup> region. Unlike the other two groups, the carboxyl hydroxyl group here have no intramolecular interactions, and can be viewed as being "free". Since the first and third groups show very similar stretching frequencies, it is obvious that the intramolecular interactions present in the conformers of the first group are fairly weak. A quick inspection of the QTAIM results reveals that this is in fact, true, as no critical points were identified for said interactions.



Figure 3.7 Zoomed in sections of the hydroxyl stretching bands for  $\alpha$ -serine in solid parahydrogen. The legend shown in Figure A (top right) is the same for all of the figures shown within. The T<sub>Sub</sub> = 430 K spectrum has been artificially situated above the other spectra in B through E such that the larger amounts of noise do not interfere with observing other spectral features.

Table	3.3	Experimental	assignment	of	the	mid-IR	vibrational	bands	for	$\alpha$ -serine	in	solid
parahy	drog	gen.										

	Assignment		GVPT2							
Assignment		So	olid Para	hydroge	en <sup>b</sup>	Arg	on <sup>c</sup>	MP2		
Conf.	Mode <sup>a</sup>	$\nu_{p\mathrm{H}_2}$	$A_{pH_2}$	$\mathbf{h}_{p\mathbf{H}_2}$	FWHM	$\nu_{\rm Ar}$	<i>I</i> <sub>Ar</sub>	$\nu_{\mathrm{MP2}}$	I <sub>MP2</sub>	
8	ν(0H) <sub>0H</sub>	3667.7	0.001	0.002	0.32	-		3693.2	45	
15	$\nu(OH)_{OH}$	3666.8	0.006	0.006	0.71	-		3696.9	46	
6	ν(0H) <sub>0H</sub>	3666.1	0.011	0.005	1.58	3658.1	S	3689.4	50	
10	ν(0H) <sub>0H</sub>	3638.1	0.021	0.004	3.21	-		3634.9	58	
2	ν(0H) <sub>0H</sub>	3630.1	0.058	0.008	4.38	3626.2	S	3647.8	46	
7	ν(OH) <sub>OH</sub>	3614.7	0.044	0.004	6.38			3616.3	60	

Assignment			Matrix Isolation								
	Assignment	So	olid Para	hydroge	e <b>n</b> <sup>b</sup>	Arge	on <sup>c</sup>	M	MP2		
Conf.	Mode <sup>a</sup>	$ u_{p\mathrm{H}_2}$	$A_{pH_2}$	$\mathbf{h}_{p\mathrm{H}_2}$	FWHM	$\nu_{\rm Ar}$	<i>I</i> <sub>Ar</sub>	$\nu_{\rm MP2}$	I <sub>MP2</sub>		
4	ν(0H) <sub>COOH</sub>	3574.5	0.310	0.040	5.00	3566.2	VS	3587.0	80		
15	$\nu(OH)_{COOH}$	3573.4	0.005	0.007	0.783	-		3583.7	65		
10	$\nu(OH)_{COOH}$	3573.2	0.096	0.016	3.57	-		3577.5	76		
5	$\nu(OH)_{COOH}$	3564.0	0.164	0.050	2.17	3561.0	S	3577.5	76		
1	$\nu(OH)_{COOH}$	3562.0	0.304	0.050	3.95	3556.8	S	3577.5	71		
1	$\nu(OH)_{OH}$	3542.0				3540.4	w	3544.5	66		
4	$\nu(OH)_{OH}$	3527.0	0.053	0.003	11.61	3538.6	w	3546.0	58		
5	$\nu(OH)_{OH}$	25126	0.012	0.002	512	3516.9	w	3551.2	66		
3	$\nu(OH)_{OH}$	5512.0	0.015	0.002	5.15	3518.6	S	3528.4	112		
1	$\nu(\mathrm{NH_2})_{\mathrm{sym}}$	3440.6	0.024	0.002	7.34	-		3450.1	11		
2	$\nu(\mathrm{NH_2})_{\mathrm{sym}}$	3434.4	0.019	0.006	2.14	-		3457.3	14		
3	$\nu(\mathrm{NH_2})_{\mathrm{sym}}$	3426.9	0.001	0.002	0.42	-		3462.5	12		
4	$\nu(\rm NH_2)_{asym}$	3423.8	0.008	0.004	1.71	3426.4	w	3473.3	16		
2	$\nu(\rm NH_2)_{asym}$	3421.6	0.037	0.004	6.73	3418.6	vw	3457.3	25		
6	$\nu(\rm NH_2)_{asym}$	3421.6	0.030	0.004	6.73	3406.0	m	3448.0	20		
1	$\nu(\rm NH_2)_{asym}$	3411.5	0.031	0.008	2.44	3403.6	w	3450.1	11		
3	$\nu(\mathrm{NH_2})_{\mathrm{sym}}$	3345.5	0.005	0.001	2.57	3317.6	vs	3373.1	1		
6	$\nu(\mathrm{NH_2})_{\mathrm{sym}}$	3328.0	0.002	0.002	0.57	33179	VC	3377.3	8		
2	$\nu(\mathrm{NH_2})_{\mathrm{sym}}$	5520.7	0.002	0.002	0.57	] 3317.5	v 3	3364.4	7		
8	$\nu(OH)_{COOH}$	3263.1	0.167	0.002	47.60	-		3235.6	237		
3	$\nu(OH)_{COOH}$	3230.4	0 341	0 004	50.02	] -		3227.0	191		
6	$\nu(OH)_{COOH}$	5250.4	0.511	0.004	50.02	] -		3202.7	241		
2	$\nu(OH)_{COOH}$	3187.6	0.372	0.008	30.12	-		3203.6	210		
1	$\nu(CH_2)_{asym}$	2992.7	0.013	0.003	3.32	] -		3030.2	18		
4	$\nu(CH_2)_{asym}$					] -		3037.8	15		
2	$\nu(CH_2)_{asym}$	29873	0.027	0.005	3 79	] -		3003.0	28		
3	$\nu(CH_2)_{asym}$	2707.5	0.027	0.005	5.7 5	] -		2995.3	27		
1	$\nu(CH_2)_{sym}$	2982.2	0.032	0.003	6.70	-		3002.9	6		
		2975.4	0.011	0.001	5.91	-					
2	$\nu(C_4H)$	29724	0.028	0.004	4 57			2961.9	10		
3	$\nu(C_4H)$	2772.1	0.020	0.001	1.57	] -		2977.7	10		
15	$\nu(C_4H)$	2963.1	0.056	0.003	11 19			2966.7	16		
7	$\nu(C_4H)$	2703.1	0.050	0.005	11.17	] -		2976.1	17		
7	$\nu(CH_2)_{sym}$	2952.6	0.056	0.005	7.77	-		2968.0	28		
	-	2944.7	0.021	0.002	6.04	-					
	-	2938.4	0.073	0.006	7.89	-					
4	$\nu(CH_2)_{sym}$	2928.6	0.077	0.003	15.25	-		2924.0	20		
6	$\nu(CH_2)_{sym}$	29191	0.010	0.001	6.44			2919.0	16		
10	$\nu(CH_2)_{sym}$	L/1/.1	0.010	0.001	0.11	] -		2901.5	22		
4	$\nu(C_4H)$	2891.9	0.006	0.002	2.5	-		2899.6	38		
5	$\nu(CH_2)_{sym}$	2888.6	0.018	0.003	42			2887.1	35		
3	$\nu(CH_2)_{sym}$	2000.0	0.010	0.000		J -		2877.7	10		
	Assignment			Matrix	Isolation	1		GVPT2			
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	Assignment	So	olid Para	hydroge	en <sup>b</sup>	Arge	on <sup>c</sup>	M	P2		
Conf.	Mode <sup>a</sup>	$\nu_{p\mathrm{H}_2}$	$A_{pH_2}$	$\mathbf{h}_{p\mathrm{H}_2}$	FWHM	$\nu_{\rm Ar}$	<i>I</i> <sub>Ar</sub>	$\nu_{\mathrm{MP2}}$	I <sub>MP2</sub>		
1	$\nu(C_4H)$	2882.5	0.089	0.005	11.5	-		2885.6	33		
	-	2857.9	0.136	0.008	11.2	-					
8	$\nu(C = 0)$	1803.9	0.023	0.003	5.78	-		1811.0	107		
2	$\nu(C = 0)$	1700.2	0.275	0.042	4 1 5	1789.2	vs	1801.6	66		
15	$\nu(C = 0)$	1790.3	0.275	0.042	4.15	_		1795.4	140		
6	$\nu(C = 0)$	1782.2	0.096	0.011	5.64	1788.9	VS	1811.4	75		
4	$\nu(C = 0)$	1777.0	0.150	0.024	4 20	1778.4	VS	1788.5	136		
3	$\nu(C = 0)$	1///.9	0.156	0.024	4.20	1778.3	VS	1786.3	8		
1	$\nu(C = 0)$	177777	0 5 1 0	0 1 2 0	250	<b>1</b> 773.0	VS	1782.7	187		
5	$\nu(C = 0)$	1//2./	0.519	0.129	2.50	<b>1771.4</b>	VS	1789.5	156		
10	$\nu(C = 0)$	17555	0.262	0.001	2 2 2		•••	1768.9	130		
7	$\nu(C = 0)$	1/55.5	0.205	0.081	2.25	<b>1</b> /54.9	W	1767.2	125		
1	$\delta$ (COH) <sub>OH</sub>	1400 4	0 1 0 0	0.000	14 50	<b>1</b> 410.1	m	1420.0	22		
4	$\omega(CH_2)$	1400.4	0.199	0.009	14.59	1411.3	vw	1405.0	13		
1	$\delta$ (NCH)					1400.5	w	1405.9	11		
2	$\delta$ (COH) <sub>COOH</sub>	1399.3	0.210	0.024	5.55	1400.0	S	1413.2	66		
5	$\delta$ (COH) <sub>OH</sub>					J 1400.5	w	1415.4	21		
2	$\omega(CH_2)$	1200.2	0.000	0.007	0.11	1385.6	W	1373.5	51		
4	$\delta$ (COH) <sub>OH</sub>	1390.3	0.089	0.007	8.11	<b>_</b> 1394.9	W	1349.0	2		
3	$\delta$ (COH) <sub>COOH</sub>	1276.2	0155	0.020	2 5 7	<b>]</b> 1371.4	VS	1391.6	231		
6	$\delta$ (COH) <sub>COOH</sub>	13/6.2	0.155	0.038	2.57	1376.3	VS	1384.9	259		
2	$\delta$ (NCH)	1345.1	0.073	0.007	6.42	1344.7	m	1364.8	108		
6	$\delta(C_4C_6H)$	1341.3	0.004	0.002	1.43	1339.8	w	1346.4	14		
1	$\delta$ (COH) <sub>COOH</sub>	1331.4	0.068	0.005	8.83	1328.3	w	1334.1	7		
4	$\delta$ (COH) <sub>COOH</sub>	1308.0	0.025	0.003	4.48	1305.6	w	1317.0	11		
1	$\delta(C_4C_6H)$	1277.6	0.006	0.001	4.13	1278.9	w	1273.6	5		
1	$\omega(CH_2)$	17676	0.066	0.002	12 27	1264.8	vw	1219.2	5		
5	$\delta(\mathrm{NH}_2)_{\mathrm{twis}}$	1207.0	0.000	0.005	12.27	1265.1	w	1266.9	12		
3	$\nu(C-0)_{COOH}$	12024	0 1 0 2	0.007	1754	1202.0	w	1205.3	4		
6	$\delta$ (COH) <sub>OH</sub>	1203.4	0.105	0.007	17.54	1208.9	m	1205.3	6		
4	$\delta(\mathrm{NH_2})_{\mathrm{twis}}$	1185.7	0.012	0.002	4.03	1186.1	vw	1187.2	10		
5	$\delta(C_4C_6H)$	1164.0	0.060	0.011	1 1 E	1168.0	m	1169.3	7		
1	-	1104.9	0.009	0.011	4.15	1162.8	S	1163.7	9		
1	$\delta(\mathrm{NH}_2)_{\mathrm{twis}}$	1151.0	0.047	0.012	2 1 2	1149.6	S	1154.6	62		
5	$\nu(C-0)_{COOH}$	1151.0	0.047	0.012	2.42	1149.6	S	1132.1	106		
10	-	1139.1	0.174	0.024	4.63			1131.3	139		
2	$\delta(\mathrm{NH}_2)_{\mathrm{twis}}$					1139.7	W	1158.9	7		
7	-	1130.2	0.319	0.019	10.24	1136.0	W	1124.8	36		
4	$\nu(C-0)_{COOH}$					<b>J</b> 1137.4	S	1132.7	30		
4	$\nu(C_4 - N)$	1112.3	0.062	0.016	2.50	1107.8	VS	1115.3	25		
1	$\nu(C-O)_{COOH}$	1108.8	0.300	0.084	2.28	1105.5	VS	1107.7	171		
5	$\nu(C_4 - N)$	1099.8				1105.4	S	1131.8	9		

	A			Matrix	Isolation	ı			GVI	PT2
	Assignment	So	olid Para	hydrog	en <sup>b</sup>		Argo	on <sup>c</sup>	M	P2
Conf.	Mode <sup>a</sup>	$ u_{p\mathrm{H}_2}$	$A_{pH_2}$	$\mathbf{h}_{p\mathrm{H}_2}$	FWHM		$\nu_{\rm Ar}$	<i>I</i> <sub>Ar</sub>	$\nu_{\mathrm{MP2}}$	I <sub>MP2</sub>
2	$\nu(C_4 - C_6)$	1093.2	0.047	0.015	1.95		1095.4	m	1101.8	36
3	$\nu(C-0)_{OH}$	1072.2	0.007	0.014	2.07	1	-		1083.0	60
5	$\nu(C-0)_{OH}$	1072.2	0.087	0.014	3.97	ſ	1073.5	VS	1072.4	93
1	$\nu(C-0)_{OH}$	1066.2	0.320	0.048	4.21		1066.2	VS	1073.5	82
15	$\nu(C-0)_{OH}$	1064.6	0.019	0.009	1.38		-		1050.3	50
4	$\nu(C-0)_{OH}$	1054.7	0.039	0.018	1.42		1056.3	S	1067.2	78
6	$\nu(C-0)_{OH}$	1058.9	0.063	0.021	1.93		1056.9	S	1061.0	55
3	$\nu(C-0)_{OH}$	1044.2	0.181	0.007	16.32		1042.4	S	1083.0	60
3	$\nu(C_4 - C_6)$	1031.7	0.004	0.001	1.91		1037.7	S	1047.4	68
6	$\omega(CH_2)$	995.1	0.003	0.005	0.41		1002.8	w	1061.0	55
2	$\nu(C-0)_{OH}$	975.9	0.025	0.015	1.05		975.2	m	982.8	43
6	$\nu(C_4 - C_6)$	942.9	0.025	0.006	2.51		942.7	m	950.7	49
5	$\omega(\rm NH_2)$	932.7	0.040	0.003	9.75		932.6	S	909.8	77
1	$\omega(\rm NH_2)$	928.3	0.040	0.007	3.84		927.0	w	940.6	41
2	$\omega(\rm NH_2)$	915.3	0.034	0.005	4.08		914.5	w	908.4	61
1	$\nu(C_4 - C_6)$	901.3	0.052	0.006	5.57		-		893.4	19
4	-	-					899.4	vw	908.2	18
3	-	074.0	0.025	0.000	1 70	1	871.1	w	907.1	114
6	$\nu(C_4 - C_6)$	8/4.0	0.025	0.009	1.70	ſ	872.8	m	859.9	21
4	$\nu(C_4 - C_6)$	863.1	0.037	0.005	4.82		860.6	S	871.6	101
2	$\tau(OH)_{COOH}$	847.7	0.053	0.010	3.30		846.4	w	841.6	15
3	-	832.4	0.024	0.005	3.10		832.2	S	754.1	73
6	-	824.0	0.014	0.006	1.47		824.2	w	799.7	64
1	$\nu(C_4 - N)$	819.0	0.334	0.041	5.20		817.5	VS	838.3	106
5	$\omega(\rm NH_2)$					1	0150		814.5	106
6	$\nu(C_4 - N)$					ſ	815.9	VS	799.7	64
4	$\omega(\rm NH_2)$	784.5	0.046	0.009	3.12		784.8	S	808.8	54
4	$\tau(OH)_{COOH}$	748.4	0.045	0.024	1.21		747.5	S	751.2	34
6	-	725 7	0.026	0.011	1 40	l	725.3	w	735.3	19
5	$\tau(OH)_{COOH}$	/25./	0.026	0.011	1.48	ſ	722.2	w	734.5	7
1	$\tau(OH)_{COOH}$	718.6	0.077	0.010	4.67		721.8	w	728.5	20

<sup>a</sup> Total energy distribution for each normal mode can be found in the Appendix. <sup>b</sup> Italicized frequencies indicate that the band cannot be definitively assigned due to overlap with strong impurity bands. <sup>c</sup> Argon assignments are taken from Najbauer *et al.* (reference 23).

It is well known that amino acids are thermally instable and readily decompose, which is evident by the presence of a number of different impurities present in the experimental spectrum. All other studies of gas-phase neutral amino acids also contain these impurities, and it is essential to find the optimal sublimation temperature, at which, one maximizes the amount of neutral amino acid, while minimizing the amount of thermal decomposition. The thermal decomposition products for  $\alpha$ -serine present in our experimental spectrum include ammonia, NH<sub>3</sub>, carbon dioxide, CO<sub>2</sub>, and water, H<sub>2</sub>O. Vibrational frequencies for these molecules in solid parahydrogen have been thoroughly studied,<sup>113</sup> and as such, it is easy for one to distinguish between bands corresponding to those products, and those corresponding to  $\alpha$ -serine. Multiple previous investigations on  $\alpha$ serine in argon and nitrogen matrices have indicated the presence of ethanolamine as a thermal product.<sup>19,20,21,23</sup> In order to ensure that vibrational bands belonging to ethanolamine were not accidentally assigned to  $\alpha$ -serine, the experimental spectrum of ethanolamine in solid parahydrogen was recorded and has been tentatively assigned. From this spectrum, it is clear that no ethanolamine is present in the  $\alpha$ -serine spectrum, and the spectrum can be found in Appendix B. Hence, we are confident that all spectral bands assigned to  $\alpha$ -serine do, in fact, come from the conformers of  $\alpha$ -serine. Unfortunately, with experimental spectra as complex as the ones presented in this section, one can never be absolutely certain of every band assigned. That being said, as discussed above, all possible measures were taken to ensure that the assignment is as accurate as possible. It should be noted that the Brendan Moore generously recorded and provided the experimental spectrum of ethanolamine.

In total ten conformers of  $\alpha$ -serine have been identified in the solid parahydrogen matrix, including the first experimental detection of conformer 15. Jarmelo *et al.* also identified conformer 9, which has not been experimentally observed in any other experiments, and based on the Boltzmann percentage, it was not expected to be observed here.<sup>20</sup> However, based on their assignment of conformer 9, it is possible that conformer 15 was present in their experimental spectrum and accidentally assigned as conformer 9, due to the fact that conformer 15 was not discovered until 11 years after the publication of this study. Additionally, according to the relative Gibb's free energies, conformers 1 and 2 should be in the largest abundance, however, the most intense bands have been assigned to conformers 1 and 4. This is in agreement with previous studies, and likely arises as a result of the weaker absorptions displayed by conformer 2.

## 3.2.3. $\alpha$ -serine Conformational Dependence on Sublimation Temperature

Spectral figures presented in the previous section show that  $\alpha$ -serine has little conformational dependence on sublimation temperature. However, as seen in Table 3.4, the relative Gibbs free energies do change a fair bit with the corresponding change in temperature. Due to the large number of overlapping peaks, it is extremely difficult to correlate the change in peak area with the

change in conformational distribution. That being said, the thermal decomposition of serine increases substantially in the 430 K spectrum compared to that observed in the 420 K spectrum. An investigation into this behavior is currently ongoing.

Table 3.4 Tabulation of the relative Gibbs free energies at 400, 410, 420, and 430 K for the 15 lowest energy conformers of  $\alpha$ -serine.

а	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
400 K	0.00	1.30	5.11	3.14	5.83	7.83	6.01	7.46	8.63	6.73	6.65	8.72	10.36	14.08	6.40
410 K	0.00	1.38	5.23	3.19	5.80	7.88	6.05	7.46	8.70	6.72	6.62	8.66	10.31	14.03	6.36
420 K	0.00	1.46	5.34	3.24	5.77	7.93	6.09	7.47	8.77	6.70	6.59	8.59	10.27	13.98	6.33
430 K	0.00	1.54	5.45	3.29	5.74	7.99	6.13	7.48	8.83	6.69	6.56	8.53	10.22	13.93	6.29

<sup>a</sup> Anharmonic thermochemical corrections were calculated as described in the main text with MP2. Electronic energies were calculated at the CCSD(T)-F12/cc-pVTZ-F12 level of theory. The temperature values in the right most column denote the relative Gibb's free energy at that temperature.

### **3.3.** Excited State Dynamics of $\alpha$ -alanine

### **3.3.1.** Computational Procedures for $\alpha$ -alanine

The basis of the computational methods employed here are described in detail in Section 2 of this thesis. This section details the computational methods and experimental techniques required to perform the analysis, which is discussed in the following subsection.

The 13 lowest energy conformers of  $\alpha$ -alanine, as depicted in Figure 3.8, were selected from the work of Cao et al.,<sup>114</sup> were used for the re-assessment of the ground state conformational analysis. The nomenclature employed in this thesis is simply related to the relative electronic energies of the conformers. Geometry optimizations and anharmonic vibrational frequency calculations were performed on all 13 conformers at the DFT and MP2 levels of theory, with the Gaussian 16 suite of programs.<sup>77</sup> In addition, geometry optimizations and harmonic frequency calculations were performed on all 13 conformers at the CCSD and CCSD(T) levels of theory, with the CFOUR 2.1 suite of programs.<sup>105,106,107,108</sup> For the sake of consistency, all calculations were performed on the L-enantiomer of  $\alpha$ -alanine, although, the calculations between L- and D-enantiomers would yield identical results within the non-relativistic limit. The frozen core approximation was utilized in all calculations. Interestingly, all 13 conformers are local minima on the ground state PES at the CCSD(T) level of theory, indicating that the assumption that B3LYP accurately describes the physicochemical characteristics of  $\alpha$ -alanine is a bad assumption.

DFT and MP2 calculations performed for  $\alpha$ -alanine are identical to those for  $\alpha$ -serine, which were discussed in Section 3.2. In short, the B3LYP functional with the inclusion of D3 dispersion corrections<sup>78</sup> and BJ damping<sup>79</sup> was employed with the def2-TZVPD basis set for all DFT calculations.<sup>80,81</sup> Since  $\alpha$ -alanine is chemically very similar to  $\alpha$ -serine, it should come of no surprise that a pruned integration grid consisting of 175,974 points for hydrogen, and 250,974 points for carbon, nitrogen, and oxygen was required for the accurate calculation of thermochemical properties. Unlike  $\alpha$ -serine, the MP2 geometry optimizations and anharmonic frequency calculations were performed with the aug-cc-pVTZ basis set,<sup>82</sup> which, due to  $\alpha$ alanine's smaller size, was computationally more affordable. All geometry optimizations at the MP2 and DFT levels of theory were converged to an RMS force value of  $1 \times 10^{-12}$ , and the stationary points were verified through the use of an analytical hessian calculation. Once again, the Berny algorithm<sup>83</sup> was applied for geometry optimizations, and DVPT2 theory was utilized for the anharmonic corrections.<sup>84,85,86,87</sup> The ORCA 4 suite of programs<sup>89,90</sup> was employed for the calculation of highly accurate CCSD(T)-F12 energies,<sup>88</sup> utilizing the cc-pVTZ-F12,<sup>91</sup> cc-pVTZ-F12/CABS,<sup>92</sup> and cc-pVQZ/C basis sets.<sup>93</sup> To save on computational time, the RI approximation was applied to the F12 explicitly correlated terms.<sup>94</sup> CCSD(T)-F12 energies were calculated for geometries optimized at the DFT, MP2, and CCSD(T) levels of theory. Lastly, as previously mentioned, analytical CCSD(T) geometry optimizations and harmonic frequency calculations were performed with the cc-pVTZ basis set<sup>82</sup> within the CFOUR 2.1 suite of programs.

Vertical excitation energies for the five lowest lying singlet electronic excited states were calculated using the single-reference EOM-CCSD<sup>115,116</sup> method, and calculations with the SAC-CI<sup>117,118</sup> method are currently ongoing. All 13 lowest energy conformers of  $\alpha$ -alanine were considered, Figure 3.8. These calculations were performed using the CCSD(T) optimized ground state geometries. Additionally, further analysis with multi-reference coupled cluster (MRCC)<sup>119</sup> and fully internally contracted multi-reference configuration interaction (MRCI)<sup>120</sup> techniques are currently ongoing. The EOM-CCSD vertical excitation energies were calculated with the ORCA 4 suite of programs,<sup>90</sup> whereas the SAC-CI vertical excitation energies are being calculated with the Gaussian 16 suite of programs.<sup>77</sup> All calculations utilize the aug-cc-pVTZ basis set, which was described in the above section.<sup>82</sup> For the sake of comparison, vertical excitation energies were also calculated with CIS(D).<sup>121,122</sup> All CIS(D) calculations were performed with the ORCA 4 suite of programs.

Initial geometry optimizations for the three lowest lying singlet electronic excited states were calculated with the configuration interaction singles (CIS)<sup>123</sup> method. The excited state geometries were verified to be stationary states through the use of analytical harmonic frequency calculations. These geometries are currently being reoptimized at the EOM-CCSD and SAC-CI level of theory with the aug-cc-pVTZ basis set. It is worth mentioning that, unlike the vertical excitation energies, the EOM-CCSD geometry optimizations are being performed with the CFOUR 2.1 suite of programs.<sup>103</sup> Lastly, the first three singlet excited states were also characterized at the TD-DFT level of theory via an electron-hole analysis as proposed by Liu *et al.*,<sup>124</sup> utilizing the hybrid exchange-correlation functional proposed by Perdew-Burke-Ernzerhof (PBE0).<sup>125</sup> The TD-DFT calculations were performed within the ORCA 4 suite of programs, while the MultiWFN suite of programs was employed for the electron-hole analysis. All TD-DFT calculations utilized Alhrichs def2-TZVP basis set, and the grid properties were identical to those for the ground state calculations. Geometry optimizations were not performed at the TD-DFT level of theory.



Figure 3.8 Three-dimensional molecular structures of the 13 lowest energy conformers of  $\alpha$ -alanine.

### **3.3.2.** Lowest Lying Electronic States for $\alpha$ -alanine

The photodissociation observed in  $\alpha$ -alanine is consistent with the Norrish Type 1 reactions for the photolysis of carbonyl compounds. In this reaction, the initial extension of the C-C bond adjacent to the carbonyl group, is termed as  $\alpha$ -cleavage. Under collision-free conditions, such as those presented in solid parahydrogen, bond rupture is the most likely outcome of photoirradiation. However, the presence of caging effects may result in the rearrangement of excited products to form stable products further complicating the spectral assignment, although this effect is minimized through the use of a solid parahydrogen matrix. Norrish type I reactions typically proceed via a spin-allowed electronic excitation to a singlet excited state, followed by an intersystem crossing (ISC) to a near-lying dissociative triplet state. However, recent investigations<sup>29</sup> have proposed that this dissociation proceeds via the first electronically excited singlet state.

An electron-hole analysis was utilized to examine the change in electron density for each of the first three singlet excited states. Within this analysis, a single electron excitation is described as an electron leaving a "hole" going to an "electron". If said excitation can be entirely described as a HOMO LUMO transition, then the "hole" is the HOMO, and the "electron" is the LUMO. However, very few excitations can be completely represented by a single pair of molecular orbitals (MOs). As such, we will describe the transition as the sum of the weighted MO wavefunctions, which is given by the following expression:

$$\rho^{\text{hole}}(\boldsymbol{r}) = \underbrace{\sum_{i}\sum_{a}(w_{i}^{a})^{2}\chi_{i}(\boldsymbol{r})\chi_{i}(\boldsymbol{r})}_{o^{\text{hole}}} + \underbrace{\sum_{i}\sum_{j\neq i}\sum_{a}(w_{i}^{a}w_{j}^{a}\chi_{i}(\boldsymbol{r})\chi_{j}(\boldsymbol{r}))}_{o^{\text{hole}}},$$
(3.3)

$$\rho^{\text{ele}}(\mathbf{r}) = \underbrace{\sum_{i}^{occ} \sum_{a}^{virt} (w_{i}^{a})^{2} \chi_{a}(\mathbf{r}) \chi_{a}(\mathbf{r})}_{\rho_{\text{local}}^{\text{ele}}} + \underbrace{\sum_{i}^{occ} \sum_{a}^{virt} \sum_{a\neq b}^{virt} w_{i}^{a} w_{i}^{b} \chi_{a}(\mathbf{r}) \chi_{b}(\mathbf{r})}_{\rho_{cross}^{\text{ele}}}, \quad (3.4)$$

where  $\chi$  is the MO wavefunctions and *w* is the weighting coefficient. Since this analysis is based upon the electron density as opposed to the wavefunction, the "hole" and "electron" do not have phase. Due to the orthonormality requirement for MOs, the sum of the square of all configuration coefficients must be one, that is,

$$\int \rho^{\text{hole}}(\boldsymbol{r})d\boldsymbol{r} = 1, \tag{3.5}$$

$$\int \rho^{\rm ele}(\mathbf{r})d\mathbf{r} = 1. \tag{3.6}$$

This property allows one to check that the same amount of electron density is in the "hole" and the "electron", ensuring that an adequate number of MOs were considered to describe the excitation. From this it is possible to calculate the overlap through the use of the following function,

$$S(\mathbf{r}) = \sqrt{\rho^{\text{hole}}(\mathbf{r})\rho^{\text{ele}}(\mathbf{r})}.$$
(3.7)

The analysis presented within this thesis utilizes TD-DFT, and as such, one must also account for de-excitations. Doing so yields the following expressions for the local terms,

$$\rho_{local}^{\text{hole}}(\mathbf{r}) = \sum_{i}^{occ} \sum_{a}^{virt} (w_i^a)^2 \chi_i(\mathbf{r}) \chi_i(\mathbf{r}) - \sum_{a}^{virt} \sum_{i}^{occ} (w_i'^a)^2 \chi_i(\mathbf{r}) \chi_i(\mathbf{r}), \quad (3.8)$$

$$\rho_{local}^{\text{ele}}(\mathbf{r}) = \sum_{i}^{occ} \sum_{a}^{virt} (w_i^a)^2 \chi_a(\mathbf{r}) \chi_a(\mathbf{r}) - \sum_{a}^{virt} \sum_{i}^{occ} (w_i'^a)^2 \chi_a(\mathbf{r}) \chi_a(\mathbf{r}).$$
(3.9)

Similarly, the cross terms are given by the following expressions,

$$\rho_{cross}^{\text{hole}}(\mathbf{r}) = \sum_{i}^{occ} \sum_{j\neq i}^{occ} \sum_{a}^{virt} w_{i}^{a} w_{j}^{a} \chi_{i}(\mathbf{r}) \chi_{j}(\mathbf{r}) - \sum_{a}^{virt} \sum_{i}^{occ} \sum_{j\neq i}^{occ} w_{i}^{'a} w_{j}^{'a} \chi_{i}(\mathbf{r}) \chi_{j}(\mathbf{r}), \quad (3.10)$$

$$\rho_{cross}^{\text{ele}}(\mathbf{r}) = \sum_{i}^{occ} \sum_{a}^{virt} \sum_{b\neq a}^{virt} w_i^a w_i^b \chi_a(\mathbf{r}) \chi_b(\mathbf{r}) - \sum_{a}^{virt} \sum_{b\neq a}^{occ} \sum_{i}^{virt} w_i'^a w_i'^b \chi_a(\mathbf{r}) \chi_b(\mathbf{r}). \quad (3.11)$$

This analysis was performed on the four lowest energy conformers of  $\alpha$ -alanine, which can be seen below in Figure 3.9.



Figure 3.9 Electron-hole analysis for the four lowest energy conformers of  $\alpha$ -alanine. Blue mesh corresponds to the "electron", and red mesh corresponds to the "hole".

Looking at the first excited state, it is obvious that electron density is primarily moved from the bond between the carboxyl and chiral carbons, to the carboxyl carbon. This particular pattern is typical for Norrish Type 1 photodissociation's,<sup>126</sup> in which the C-C bond breaks forming two radicals, those being the HOCO and ethylamine radicals in this case. That being said, one cannot claim that photodissociation will occur based only upon an electron-hole analysis. However, to accurately model photodissociation processes one must employ multi-reference techniques. Said investigation is currently ongoing at the MRCI and MRCC levels of theory. Interestingly, the second excited state for conformers 2 and 3 show substantial loss of electron density between this same C-C bond, indicating that these conformers may undergo photodissociation forming HOCO and ethylamine radicals via either the first or second excited states. An initial look at the fourth conformer may convince the reader that it also has two dissociative states, however, the electron density is evenly distributed between both the carboxyl and chiral carbons, with the loss of electron density coming from the middle of the bond. Since the electron density is localized on the two carbons, it is highly unlikely that this state is a dissociative state. An initial investigation of the photodissociation was attempted through the use of geometry optimizations for the first three singlet excited states for all 13 low energy conformers of  $\alpha$ -alanine at the CIS/aug-cc-pVTZ level of theory. These optimizations indicate that the first three singlet states are bound states, in disagreement with the previous results<sup>30</sup> obtained with TD-DFT, and further confirming the need for multi-reference techniques. That being said, photochemical processes can rarely be described by single-reference methods.

The vertical excitation energies are shown below in Table 3.5. In addition to the excitation energies, the singles character is reported for the EOM-CCSD calculations. A quick comparison of the two values indicates that CIS(D) slightly underestimates the excitation energy, which is a known downside to the CIS(D) method.<sup>122</sup> However, due to the reduced cost of CIS(D) compared to that of EOM-CCSD, the values are very good. The only experimental electronic spectrum of  $\alpha$ -alanine was recorded in methanol by Abu-Eittah *et al.* in 1988.<sup>127</sup> This spectrum, which can be found in the reference, was recorded for the 200 to 350 nm region. It contains two peaks, one at around 200 nm, starting before the spectral recording, and the second at roughly 265 nm. Unfortunately,  $\alpha$ -alanine in methanol forms a substantial number of stabilizing intermolecular interactions with the methanol. As such, it is expected that the electronic excitation levels will show a large shift. However, the experimental values are in reasonable agree with the energies calculated for the S<sub>1</sub> and S<sub>2</sub> electronic states.

		EOM-CCSD			CIS(D)	
Conf.	<b>S</b> <sub>1</sub> (eV)	<b>S</b> <sub>2</sub> (eV)	<b>S</b> <sub>3</sub> (eV)	<b>S</b> <sub>1</sub> (eV)	<b>S</b> <sub>2</sub> (eV)	<b>S</b> <sub>3</sub> (eV)
1	5.95 (90.42) <sup>a</sup>	6.68 (90.36)	7.38 (88.73)	5.85	6.42	7.17
2	5.75 (92.00)	6.69 (92.37)	7.44 (91.86)	5.65	6.45	7.18
3	5.82 (91.86)	6.75 (92.37)	7.45 (91.81)	5.71	6.51	7.05
4	5.71 (91.53)	6.41 (92.20)	7.19 (91.63)	5.60	6.14	6.96
5	5.68 (91.61)	6.45 (92.12)	7.20 (91.53)	5.58	6.18	6.94
6	6.03 (92.05)	6.43 (92.16)	7.18 (90.91)	5.91	6.17	6.92
7	5.97 (92.05)	6.29 (92.05)	7.27 (91.37)	5.87	6.02	6.98
8	5.83 (92.09)	6.39 (92.19)	7.33 (91.59)	5.74	6.12	7.16
9	5.89 (92.08)	6.42 (92.25)	7.32 (91.66)	5.78	6.16	7.01
10	5.85 (92.08)	6.65 (92.22)	7.14 (91.72)	5.76	6.41	6.74

Table 3.5 Vertical excitation energies for the first three singlet excited states for all 13 conformers of  $\alpha$ -alanine at the EOM-CCSD/aug-cc-pVTZ and CIS(D)/aug-cc-pVTZ levels of theory.

		EOM-CCSD			CIS(D)	
Conf.	<b>S</b> <sub>1</sub> (eV)	<b>S</b> <sub>2</sub> (eV)	<b>S</b> <sub>3</sub> (eV)	$\mathbf{S_1}(\mathrm{eV})$	$\mathbf{S_2} (\mathrm{eV})$	<b>S</b> <sub>3</sub> (eV)
11	5.70 (91.91)	6.11 (92.25)	7.17 (92.35)	5.59	5.86	6.85
12	5.94 (92.06)	6.48 (92.00)	7.03 (91.34)	5.83	6.23	6.68
13	5.89 (92.04)	6.32 (91.94)	7.28 (91.45)	5.80	6.08	6.9

<sup>a</sup> Values in parentheses correspond to the percentage of singles character for each of the states.

The NCI in the ground state  $\alpha$ -alanine conformers were investigated through the use of NCI and QTAIM. Projections of these analyses onto the molecular structure can be seen below in Figure 3.10 and Figure 3.11. It is evident that conformers 2 and 3 display the strongest intramolecular interactions. An initial analysis indicates that the excitation energies are not dependent on the NCIs. This is contrary to the electron-hole analysis, which showed a conformational dependence on dissociative states.



Figure 3.10 NCI analysis for the conformers of  $\alpha$ -alanine. The colour bar on the right denotes whether the interaction is attractive, repulsive, or weak, denoted by red, blue, green respectively.



Figure 3.11 Projection of QTAIM critical points onto  $\alpha$ -serine. Nuclear critical points are purple, ring critical points are blue, and bond critical points are yellow.

## 4. Conclusion

The conformational dynamics of  $\alpha$ -serine were investigated through the use of *ab initio* calculations and MI-FTIR spectroscopy with parahydrogen matrices, in which ten conformers of  $\alpha$ -serine were identified confirming the superiority of the parahydrogen matrix for studying the conformational landscape of highly flexible species. That is, only nine conformers were identified within argon matrices, which is one less than was observed here. Interestingly, ethanolamine was not observed as a thermal product, despite being categorized as one in previous studies.

The three lowest lying singlet excited states for the four lowest energy conformers of  $\alpha$ alanine were investigated through the use of an electron-hole analysis, which indicated that the first state is likely a dissociative state for all conformers. Additionally, for conformers exhibiting strong hydrogen bonds between the carboxyl hydrogen and amine lone pair, the second excited state may also be a dissociative state. All discussed dissociative states were shown to yield the HOCO and ethylamine radicals. Additionally, vertical excitation energies were calculated for all 13 low energy conformers of  $\alpha$ -alanine, in which, the CIS(D) and EOM-CCSD values appear to be in good agreement and confirmed the need for experimental data on the excited states of neutral alanine.

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# Appendices

## A. Supplemental Material for the Experimental and Computational Methods

Algorithm 1. Hartree-Fock Variational Self-Consistent Field Procedure

- 1 Input a guess of the molecular orbital coefficients.
- 2 Form the Fock matrix.
- 3 Diagonalize the Fock matrix.
- 4 Obtain the new density matrix.
- 5A If the new density matrix is not the same as the initial density matrix, repeat steps 2 through 4.
- 5B If the new density matrix is equal to the initial density matrix (within some value) then the procedure is completed.
- 6 Check the converged energies and orbital coefficients.

## **B.** Supplemental Material for the Conformational Analysis of Serine

The following section contains the raw data from the conformational analysis of L-serine presented in Section 3. This includes the full FTIR spectra taken at each sublimation temperature, the theoretically calculated infrared frequencies and their associated intensities, and the QTAIM and NCI figures for the higher energy conformers.



Figure B.1 FTIR spectrum of L-serine immediately after deposition in the solid parahydrogen matrix (flow rate = 5 ccm,  $T_{Sub}$  = 400 K,  $T_{Dep.}$  = 4 K).



Figure B.2 FTIR spectrum of L-serine immediately after deposition in the solid parahydrogen matrix (flow rate = 5 ccm,  $T_{Sub}$  = 410 K,  $T_{Dep.}$  = 4 K).



Figure B.3 FTIR spectrum of L-serine immediately after deposition in the solid parahydrogen matrix (flow rate = 5 ccm,  $T_{Sub}$  = 420 K,  $T_{Dep.}$  = 4 K).



Figure B.4 FTIR spectrum of L-serine immediately after deposition in the solid parahydrogen matrix (flow rate = 5 ccm,  $T_{Sub}$  = 430 K,  $T_{Dep.}$  = 4 K).

Table B.1 Nomenclature conversion table for the conformers of serine in select recent investigations.

Here	Allen <sup>a</sup>	Blanco <sup>b</sup>	Lambie <sup>c</sup>	Jarmelo <sup>d</sup>	Najbauer <sup>e</sup>
1	Π	Ia	1	1	1
2	Ι	IIb	2	2	2
3	III	IIc	3	3	3
4	IV	I'b	4	4	4
5	VIII	$III_{\alpha}a$	5	6	5
6	VI	IIa	-	5	6
7	V	$III_{\beta}b$	6	7	7
8	IX	-	7	8	8
9	VII	-	-	9	9
10	XII	III <sub>β</sub> c	8	-	10
11	Х	Ib	9	-	11
12	-	Ic	10	-	12
13	-	-	11	-	13
14	-	-	12	-	14
15	XI	-	-	-	-

<sup>a</sup> Reference 18. <sup>b</sup> Reference 22. <sup>c</sup> Reference 19. <sup>d</sup> References 20 and 21. <sup>e</sup> Reference 23.

gure 3.1	•				
В	Sond Length		Bond Angle		Dihedral Angle
<i>S</i> <sub>1</sub>	$r(N_1 - H_2)$	<i>S</i> <sub>14</sub>	$\theta(C_4 - N_1 - H_2)$	S <sub>26</sub>	$\tau(\mathrm{H}_2-\mathrm{N}_1-\mathrm{C}_4-\mathrm{H}_5)$
<i>S</i> <sub>2</sub>	$r(N_1 - H_3)$	<i>S</i> <sub>15</sub>	$\theta(C_4 - N_1 - H_3)$	<i>S</i> <sub>27</sub>	$\tau(\mathrm{H}_2-\mathrm{N}_1-\mathrm{C}_4-\mathrm{C}_6)$
$S_3$	$r(N_1 - C_4)$	$S_{16}$	$\theta(N_1 - C_4 - H_5)$	<i>S</i> <sub>28</sub>	$\tau(\mathrm{H}_2-\mathrm{N}_1-\mathrm{C}_4-\mathrm{C}_7)$
$S_4$	$r(C_4 - H_5)$	$S_{17}$	$\theta(N_1 - C_4 - C_6)$	<i>S</i> <sub>29</sub>	$\tau(C_7 - C_4 - N_1 - H_3)$
$S_5$	$r(C_4 - C_6)$	<i>S</i> <sub>18</sub>	$\theta(N_1 - C_4 - C_7)$	<i>S</i> <sub>30</sub>	$\tau(\mathrm{N}_1-\mathrm{C}_4-\mathrm{C}_6-\mathrm{H}_8)$
$S_6$	$r(C_4 - C_7)$	<i>S</i> <sub>19</sub>	$\theta(C_4 - C_6 - H_8)$	$S_{31}$	$\tau(\mathrm{N}_1-\mathrm{C}_4-\mathrm{C}_6-\mathrm{H}_9)$
$S_7$	$r(C_6 - H_8)$	<i>S</i> <sub>20</sub>	$\theta(C_4 - C_6 - H_9)$	<i>S</i> <sub>32</sub>	$\tau(N_1 - C_4 - C_6 - O_{10})$
$S_8$	$r(C_6 - H_9)$	<i>S</i> <sub>21</sub>	$\theta(C_4-C_6-O_{10})$	<i>S</i> <sub>33</sub>	$\tau(N_1 - C_4 - C_7 - O_{11})$
S <sub>9</sub>	$r(C_6 - O_{10})$	<i>S</i> <sub>22</sub>	$\theta(C_4-C_7-O_{11})$	$S_{34}$	$\tau(C_7 - C_4 - C_6 - O_{10})$
$S_{10}$	$r(C_7 - O_{11})$	<i>S</i> <sub>23</sub>	$\theta(\mathrm{C}_6-\mathrm{O}_{10}-\mathrm{H}_{12})$	$S_{35}$	$\tau(C_4 - C_7 - O_{13} - H_{14})$
<i>S</i> <sub>11</sub>	$r(C_7 - O_{13})$	<i>S</i> <sub>24</sub>	$\theta(C_4-C_7-O_{13})$	<i>S</i> <sub>36</sub>	$\tau(0_{13} - C_7 - C_4 - 0_{11})$
<i>S</i> <sub>12</sub>	$r(0_{10} - H_{12})$	<i>S</i> <sub>25</sub>	$\theta(\mathrm{C}_7-\mathrm{O}_{13}-\mathrm{H}_{14})$		
<i>S</i> <sub>13</sub>	$r(0_{13} - H_{14})$				

Table B.2 Definition of internal coordinates,  $S_i$ , for use in the normal mode analysis and total energy distribution reported for each normal mode. Atom numbering corresponds to that shown in Figure 3.1.

Table B.3 Conversion of internal coordinates,  $S_i$ , to those presented by He and Allen (Ref. 18).

Here	He and Allen	Here	He and Allen	Here	He and Allen
<i>S</i> <sub>1</sub>	<i>S</i> <sub>1</sub>	<i>S</i> <sub>14</sub>	S <sub>3</sub>	S <sub>26</sub>	S <sub>6</sub>
<i>S</i> <sub>2</sub>	S <sub>34</sub>	<i>S</i> <sub>15</sub>	S <sub>35</sub>	<i>S</i> <sub>27</sub>	S <sub>9</sub>
$S_3$	<i>S</i> <sub>2</sub>	<i>S</i> <sub>16</sub>	<i>S</i> <sub>5</sub>	<i>S</i> <sub>28</sub>	<i>S</i> <sub>12</sub>
$S_4$	$S_4$	<i>S</i> <sub>17</sub>	<i>S</i> <sub>8</sub>	<i>S</i> <sub>29</sub>	S <sub>36</sub>
$S_5$	<i>S</i> <sub>7</sub>	<i>S</i> <sub>18</sub>	<i>S</i> <sub>11</sub>	<i>S</i> <sub>30</sub>	<i>S</i> <sub>15</sub>
$S_6$	<i>S</i> <sub>10</sub>	<i>S</i> <sub>19</sub>	<i>S</i> <sub>14</sub>	$S_{31}$	<i>S</i> <sub>18</sub>
<i>S</i> <sub>7</sub>	<i>S</i> <sub>16</sub>	<i>S</i> <sub>20</sub>	<i>S</i> <sub>17</sub>	<i>S</i> <sub>32</sub>	<i>S</i> <sub>21</sub>
$S_8$	<i>S</i> <sub>13</sub>	<i>S</i> <sub>21</sub>	S <sub>20</sub>	<i>S</i> <sub>33</sub>	<i>S</i> <sub>24</sub>
S <sub>9</sub>	<i>S</i> <sub>19</sub>	<i>S</i> <sub>22</sub>	S <sub>23</sub>	<i>S</i> <sub>34</sub>	S <sub>33</sub>
$S_{10}$	S <sub>22</sub>	<i>S</i> <sub>23</sub>	S <sub>26</sub>	<i>S</i> <sub>35</sub>	<i>S</i> <sub>27</sub>
<i>S</i> <sub>11</sub>	S <sub>28</sub>	<i>S</i> <sub>24</sub>	S <sub>29</sub>	S <sub>36</sub>	<i>S</i> <sub>30</sub>
<i>S</i> <sub>12</sub>	S <sub>25</sub>	<i>S</i> <sub>25</sub>	S <sub>32</sub>		
<i>S</i> <sub>13</sub>	S <sub>31</sub>				

Table B.4 Anharmonic vibrational frequencies (cm<sup>-1</sup>) and intensities (km mol<sup>-1</sup>) for  $\alpha$ -serine conformers 1 and 2, calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory.

		S	er-1	Ser-2				
Mode	MI	22	B3LYP	-D3BJ	MP	2	B3LYP	-D3BJ
_	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>v</b> / cm <sup>-1</sup>	Int.
$\nu_1$	3577.5	71	3532.8	51	3647.8	46	3602.8	38
$\nu_2$	3544.5	66	3505.9	59	3457.3	14	3408.1	13
$\nu_3$	3450.1	11	3402.4	8	3364.4	7	3333.4	4
$ u_4 $	3366.8	7	3341.6	4	3203.6	210	3183.1	231
$\nu_5$	3030.2	18	2984.1	15	3017.8	11	2948.1	15
$\nu_6$	3002.9	6	2935.6	12	3003.0	28	2954.6	22
$\nu_7$	2885.6	33	2827.5	40	2961.9	10	2908.4	5
$\nu_8$	1782.7	187	1773.8	231	1801.6	66	1796.8	152
$\nu_9$	1595.7	23	1572.9	7	1586.0	24	1579.4	22
$\nu_{10}$	1485.6	1	1471.3	2	1467.6	8	1454.9	4
$\nu_{11}$	1420.0	22	1403.7	19	1413.2	66	1390.8	41
$v_{12}$	1405.9	11	1388.8	5	1373.5	51	1342.9	32
$\nu_{13}$	1351.5	4	1338.2	2	1364.8	108	1356.0	99
$\nu_{15}$	1334.1	7	1317.7	8	1346.0	23	1345.6	15
$v_{16}$	1273.6	5	1262.2	5	1278.2	5	1267.7	9
$v_{17}$	1219.2	5	1219.2	12	1215.7	3	1200.7	14
$\nu_{18}$	1163.7	9	1157.3	3	1197.2	13	1169.3	13
$\nu_{19}$	1154.6	62	1126.9	56	1158.9	7	1150.1	5
$\nu_{20}$	1107.7	171	1086.6	98	1101.8	36	1078.2	37
$v_{21}$	1073.5	82	1050.1	68	1073.0	9	1051.6	17
$v_{22}$	1011.4	4	996.6	2	982.8	43	964.5	74
$v_{23}$	940.6	41	909.2	22	925.8	21	911.0	2
$\nu_{24}$	893.4	19	870.6	52	761.4	48	873.6	89
$\nu_{25}$	838.3	106	806.3	116	908.4	61	738.4	53
$v_{26}$	728.5	20	722.9	4	841.6	15	825.8	3
$v_{27}$	658.3	10	657.6	14	764.8	6	759.5	10
$\nu_{28}$	578.0	75	547.8	32	594.8	4	586.3	3
$v_{29}$	488.4	69	439.5	82	553.4	5	543.5	5
$\nu_{30}$	550.5	28	581.3	69	511.0	3	509.2	3
$\nu_{31}$	407.9	21	403.8	18	279.1	58	270.3	73
$v_{31}$	345.2	2	334.9	1	420.9	13	422.8	7
$v_{32}$	307.8	2	316.1	2	361.9	18	329.3	21
$\nu_{33}$	210.8	6	154.7	8	298.5	15	288.5	13
$v_{34}$	178.9	6	211.7	1	225.9	3	221.1	2
$\nu_{35}$	133.5	10	124.2	10	108.6	8	102.8	7
$v_{36}$	54.0	1	50.5	1	69.8	4	69.2	6

Table B.5 Anharmonic vibrational frequencies (cm<sup>-1</sup>) and intensities (km mol<sup>-1</sup>) for  $\alpha$ -serine conformers 5 and 4, calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory.

		S	er-3			Ser-4			
Mode	MI	22	B3LYP	-D3BJ	MP	2	B3LYP	-D3BJ	
	<b>v</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	
$\nu_1$	3528.4	112	3471.2	135	3587.0	80	3546.9	65	
$\nu_2$	3462.5	12	3412.7	9	3546.0	58	3513.1	48	
$\nu_3$	3373.1	1	3343.8	0	3473.3	16	3428.7	20	
$ u_4 $	3227.0	192	3203.6	212	3380.7	12	3352.8	7	
$\nu_5$	2995.3	27	2904.9	21	3037.8	15	2978.6	19	
$\nu_6$	2977.7	10	2919.9	10	2924.0	20	2866.5	38	
$\nu_7$	2877.7	27	2813.4	50	2899.6	38	2828.7	50	
$\nu_8$	1786.3	8	1779.1	98	1788.5	136	1775.2	128	
$\nu_9$	1567.2	7	1635.3	34	1569.9	3	1623.7	22	
$\nu_{10}$	1481.5	0	1471.3	1	1482.6	2	1466.3	1	
$\nu_{11}$	1436.0	14	1416.2	9	1417.8	13	1404.0	15	
$v_{12}$	1391.6	231	1344.9	60	1405.0	35	1382.4	16	
$v_{13}$	1358.1	93	1367.0	58	1349.9	2	1338.2	1	
$v_{15}$	1347.3	4	1340.9	53	1317.0	11	1298.3	9	
$v_{16}$	1281.1	4	1279.8	9	1275.8	1	1261.0	3	
$v_{17}$	1212.2	2	1200.5	2	1205.8	7	1200.0	22	
$\nu_{18}$	1205.3	4	1178.8	7	1187.2	10	1179.5	11	
$v_{19}$	1163.7	2	1161.0	8	1132.7	30	1122.4	101	
$\nu_{20}$	1110.4	4	1082.2	10	1115.3	25	1090.9	46	
$v_{21}$	1083.0	60	1058.8	106	1067.2	78	1042.1	85	
$v_{22}$	1047.4	68	1014.8	42	994.6	1	979.9	1	
$v_{23}$	985.7	12	979.0	16	908.2	18	884.7	14	
$v_{24}$	907.1	114	884.7	70	871.6	101	838.6	24	
$\nu_{25}$	754.1	73	727.5	34	808.8	54	772.3	59	
$v_{26}$	810.4	1	792.6	7	751.2	34	740.1	58	
$v_{27}$	733.5	5	733.1	5	621.1	57	614.1	52	
$\nu_{28}$	476.5	84	684.2	1	655.4	21	619.4	10	
$\nu_{29}$	663.7	6	433.6	88	472.3	35	485.7	22	
$\nu_{30}$	548.8	4	541.3	3	524.4	31	515.3	32	
$\nu_{31}$	418.9	3	416.7	2	478.7	42	449.8	118	
$\nu_{31}$	381.5	7	375.5	9	365.0	2	359.2	3	
$v_{32}$	328.8	21	325.2	13	296.1	4	251.0	6	
$v_{33}$	246.1	18	242.7	14	230.1	15	309.2	5	
$v_{34}$	229.9	14	227.5	14	191.4	21	138.5	7	
$\nu_{35}$	162.3	4	152.6	4	109.7	5	103.3	5	
<i>v</i> <sub>36</sub>	62.7	2	63.4	2	69.5	1	68.4	1	

Table B.6 Anharmonic vibrational frequencies (cm<sup>-1</sup>) and intensities (km mol<sup>-1</sup>) for  $\alpha$ -serine conformers 5 and 4, calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory.

		Se	er-5			Ser-6		
Mode	MI	22	B3LYP	-D3BJ	MP	2	B3LYP	-D3BJ
	<b>v</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.
$\nu_1$	3577.5	76	3538.7	60	3689.4	50	3642.7	42
$\nu_2$	3551.2	66	3511.7	56	3448.0	20	3399.4	16
$\nu_3$	3462.7	10	3414.6	8	3377.3	8	3352.2	2
$ u_4 $	3382.1	5	3357.4	2	3202.7	241	3180.8	193
$\nu_5$	3026.1	14	2982.2	13	3003.3	14	2924.3	24
$\nu_6$	3006.8	5	2951.1	8	2977.2	8	2906.4	8
$\nu_7$	2887.1	35	2834.9	36	2919.0	16	2871.9	19
$\nu_8$	1789.5	156	1773.4	127	1811.4	75	1809.7	98
$\nu_9$	1580.0	8	1600.4	8	1604.4	10	1597.9	23
$\nu_{10}$	1486.4	1	1472.0	2	1490.7	3	1475.0	4
$\nu_{11}$	1415.4	21	1398.0	26	1420.6	1	1404.2	1
$v_{12}$	1377.6	9	1367.6	11	1384.9	259	1356.1	32
$v_{13}$	1345.6	0	1332.1	2	1346.4	14	1335.6	19
$\nu_{15}$	1298.9	32	1332.3	5	1310.5	3	1290.1	1
$v_{16}$	1266.9	12	1260.1	25	1282.0	8	1278.7	13
$v_{17}$	1247.9	1	1244.4	9	1227.6	5	1216.6	14
$\nu_{18}$	1169.3	7	1160.7	8	1205.3	6	1177.0	4
$\nu_{19}$	1132.1	106	1112.9	79	1165.0	12	1150.6	13
$\nu_{20}$	1131.8	9	1098.2	7	1103.5	40	1078.5	37
$v_{21}$	1072.4	93	1048.9	52	1061.0	55	1030.4	57
$\nu_{22}$	1001.9	5	987.7	1	1011.1	14	993.5	12
$v_{23}$	909.8	77	878.2	34	950.7	49	924.7	45
$v_{24}$	897.2	15	868.6	26	920.9	54	859.8	71
$\nu_{25}$	814.5	106	777.8	118	799.7	64	897.4	11
$v_{26}$	735.3	19	730.0	16	859.9	21	750.6	60
$v_{27}$	661.9	27	649.3	28	734.5	5	726.5	9
$\nu_{28}$	557.2	41	548.7	37	649.1	7	646.8	8
$\nu_{29}$	459.5	69	593.0	3	557.3	6	553.7	8
$\nu_{30}$	587.7	19	432.1	74	422.8	9	417.5	6
$\nu_{31}$	412.7	11	406.8	11	402.5	10	340.2	6
$\nu_{31}$	345.9	2	337.0	2	288.3	37	269.0	41
$v_{32}$	297.4	9	284.1	2	320.6	2	363.5	9
$v_{33}$	235.7	5	235.7	8	194.5	72	153.4	61
$v_{34}$	182.0	2	184.7	2	192.6	12	199.5	8
$\nu_{35}$	134.4	5	127.7	4	135.9	9	127.3	10
v <sub>36</sub>	30.7	1	29.9	1	78.6	0	70.4	0

		S	er-7		Ser-8				
Mode	MI	P2	B3LYP	-D3BJ	MI	22	B3LYP	-D3BJ	
	<b>v</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	
$\nu_1$	3616.3	60	3553.5	60	3693.2	45	3645.9	29	
$\nu_2$	3575.5	75	3528.2	57	3452.4	12	3407.9	9	
$\nu_3$	3458.2	11	3414.4	9	3369.6	1	3339.1	0	
$ u_4 $	3369.0	3	3342.7	4	3235.6	237	3191.7	223	
$\nu_5$	3029.5	16	2966.6	21	3008.1	14	2922.4	18	
$\nu_6$	2968.0	28	2911.8	28	2975.6	9	2911.6	1	
$\nu_7$	2976.1	17	2855.4	22	2909.7	24	2860.2	27	
$\nu_8$	1767.2	125	1751.9	21	1811.0	107	1802.8	140	
$\nu_9$	1573.9	9	1624.3	11	1600.6	25	1592.0	23	
$\nu_{10}$	1468.4	6	1455.8	3	1492.4	2	1478.2	3	
$\nu_{11}$	1408.2	22	1398.3	7	1416.8	2	1403.7	0	
$v_{12}$	1382.8	20	1366.5	6	1388.4	54	1349.2	245	
$\nu_{13}$	1370.4	14	1350.3	11	1359.1	75	1374.8	42	
$\nu_{15}$	1353.4	5	1348.5	12	1292.2	13	1285.6	9	
$v_{16}$	1286.0	1	1250.2	7	1257.5	3	1243.8	7	
$v_{17}$	1229.9	5	1219.4	9	1214.8	10	1189.8	8	
$\nu_{18}$	1174.9	0	1169.8	0	1191.1	5	1169.5	8	
$v_{19}$	1124.8	36	1109.7	234	1168.4	3	1156.5	5	
$v_{20}$	1117.4	41	1092.0	27	1108.1	20	1083.4	17	
$v_{21}$	1052.1	6	1025.2	10	1078.9	18	1050.8	22	
$v_{22}$	998.7	31	982.4	48	1041.7	86	1012.5	81	
$v_{23}$	916.4	9	892.7	2	949.9	38	933.0	39	
$v_{24}$	851.9	84	807.5	35	885.4	74	897.9	71	
$v_{25}$	826.6	50	781.7	110	905.5	6	842.2	10	
$v_{26}$	747.4	26	748.4	23	755.6	54	740.2	30	
$v_{27}$	699.1	13	693.9	16	727.4	6	725.4	6	
$\nu_{28}$	572.4	94	577.9	91	612.5	15	610.3	10	
$\nu_{29}$	646.8	47	644.0	45	525.1	0	521.3	1	
$\nu_{30}$	407.8	118	416.7	121	425.2	8	420.6	6	
$v_{31}$	387.8	5	376.3	6	388.2	11	366.1	2	
$\nu_{31}$	396.9	10	394.6	7	320.3	7	309.7	10	
$v_{32}$	274.6	9	242.1	22	344.2	44	214.2	10	
$\nu_{33}$	243.9	14	259.9	2	114.7	52	118.2	52	
$\nu_{34}$	218.8	1	213.3	1	189.2	12	321.8	34	
$\nu_{35}$	159.4	8	151.1	8	119.2	12	115.7	11	
$v_{36}$	40.0	1	38.9	1	63.2	2	57.1	1	

Table B.7 Anharmonic vibrational frequencies (cm<sup>-1</sup>) and intensities (km mol<sup>-1</sup>) for  $\alpha$ -serine conformers 7 and 8, calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory.
Table B.8 Anharmonic vibrational frequencies (cm<sup>-1</sup>) and intensities (km mol<sup>-1</sup>) for  $\alpha$ -serine conformers 9 and 10, calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory.

	Ser-9				Ser-10			
Mode	MP2 B3LYP-D3B			-D3BJ	MP2 B3LYP			-D3BJ
_	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.
$\nu_1$	3673.8	38	3621.4	31	3634.9	58	3584.0	46
$\nu_2$	3449.2	20	3400.0	15	3577.5	76	3534.3	56
$\nu_3$	3376.7	11	3352.0	3	3455.2	3	3410.3	0
$ u_4 $	3217.6	251	3201.4	181	3371.1	2	3348.3	1
$\nu_5$	3021.3	13	2955.2	18	3031.6	17	2969.6	19
$\nu_6$	3001.1	17	2876.6	15	2983.1	18	2925.5	16
$\nu_7$	2952.5	12	2889.3	12	2901.5	22	2854.1	31
$\nu_8$	1807.0	106	1795.7	227	1768.9	130	1754.3	232
$\nu_9$	1598.0	24	1629.1	6	1570.6	21	1640.6	12
$\nu_{10}$	1478.5	3	1465.2	3	1476.6	2	1460.0	4
$\nu_{11}$	1376.3	252	1384.0	183	1399.4	15	1395.0	15
$v_{12}$	1397.2	12	1350.8	262	1377.4	3	1358.0	4
$v_{13}$	1352.6	13	1344.9	0	1364.4	24	1343.6	8
$v_{15}$	1333.8	8	1323.2	22	1355.2	3	1340.7	13
$v_{16}$	1284.0	2	1280.4	3	1280.6	12	1265.9	13
$v_{17}$	1248.4	1	1244.4	1	1226.7	5	1215.3	17
$\nu_{18}$	1200.8	13	1172.8	23	1171.0	2	1156.8	4
$\nu_{19}$	1132.3	14	1117.1	25	1131.3	139	1115.6	183
$\nu_{20}$	1107.0	37	1085.7	21	1117.9	72	1082.2	19
$v_{21}$	1057.5	42	1029.7	95	1080.1	23	1048.5	108
$v_{22}$	990.6	15	976.4	9	1020.3	19	1003.5	22
$v_{23}$	942.8	19	911.3	36	987.4	3	971.3	5
$v_{24}$	902.5	26	868.7	61	838.6	126	833.8	13
$v_{25}$	781.2	65	880.2	28	807.6	40	735.6	129
$v_{26}$	883.0	49	741.9	60	738.0	11	733.3	10
$v_{27}$	721.4	10	716.6	12	642.1	19	647.1	12
$\nu_{28}$	653.5	4	647.5	3	544.1	52	527.0	78
$\nu_{29}$	557.9	2	553.9	2	607.3	48	603.9	25
$\nu_{30}$	424.5	3	423.1	23	375.4	79	338.0	105
$v_{31}$	306.5	58	391.1	4	448.3	6	447.8	6
$v_{31}$	359.6	21	333.4	3	289.7	6	286.4	4
$v_{32}$	416.1	21	253.3	16	368.5	1	356.5	2
$v_{33}$	184.5	39	221.5	100	168.8	28	176.8	25
$v_{34}$	188.4	7	191.8	8	208.5	1	203.8	1
$v_{35}$	133.2	12	123.5	13	159.7	2	143.8	3
$v_{36}$	81.3	3	76.1	2	44.9	1	40.9	2

Table B.9 Anharmonic vibrational frequencies (cm<sup>-1</sup>) and intensities (km mol<sup>-1</sup>) for  $\alpha$ -serine conformers 11 and 12, calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory.

		Se	r-11		Ser-12				
Mode	MP2 B3LYP-D3BJ			-D3BJ	MP2 B3LYP-D3BJ				
_	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	
$\nu_1$	3674.3	34	3624.4	26	3653.1	48	3597.0	39	
$\nu_2$	3573.7	65	3531.2	45	3566.3	86	3522.8	62	
$\nu_3$	3437.6	10	3394.0	8	3442.5	5	3397.0	5	
$ u_4 $	3368.6	3	3344.1	2	3372.8	2	3352.3	1	
$\nu_5$	3034.5	11	2971.9	15	3032.8	11	2988.2	9	
$\nu_6$	3004.9	24	2957.9	27	2989.8	9	2922.0	13	
$\nu_7$	2940.7	10	2866.3	7	2891.6	30	2840.7	38	
$\nu_8$	1791.0	160	1780.6	237	1790.4	93	1785.9	124	
$\nu_9$	1604.3	15	1604.8	11	1603.0	15	1655.2	2	
$\nu_{10}$	1469.4	3	1459.8	4	1488.6	1	1472.2	0	
$\nu_{11}$	1388.8	12	1378.6	7	1406.2	18	1395.6	13	
$v_{12}$	1369.7	9	1357.1	5	1377.4	2	1369.9	0	
$v_{13}$	1357.1	2	1341.4	2	1353.9	8	1335.7	5	
$\nu_{15}$	1337.7	0	1319.2	3	1302.2	9	1283.5	6	
$v_{16}$	1278.3	1	1270.5	2	1251.3	6	1244.9	3	
$v_{17}$	1239.5	2	1224.5	4	1211.6	4	1202.2	11	
$\nu_{18}$	1171.4	14	1166.5	15	1188.4	1	1176.7	7	
$v_{19}$	1131.7	48	1116.5	35	1143.6	13	1118.0	23	
$\nu_{20}$	1105.9	203	1084.6	203	1101.4	214	1081.6	198	
$v_{21}$	1047.2	23	1018.9	30	1075.0	29	1038.6	40	
$v_{22}$	996.2	47	976.0	49	1017.8	5	1001.5	13	
$v_{23}$	908.7	60	878.5	6	985.6	2	959.8	4	
$v_{24}$	893.8	77	848.2	233	868.2	133	813.3	163	
$\nu_{25}$	831.0	10	816.6	14	792.2	10	771.6	5	
$v_{26}$	737.3	11	732.1	21	735.7	8	730.7	12	
$v_{27}$	632.1	82	622.6	67	669.6	5	656.8	6	
$\nu_{28}$	590.1	15	581.0	21	560.0	24	554.5	79	
$v_{29}$	500.5	19	491.4	18	512.9	21	508.2	31	
$v_{30}$	475.1	7	471.5	13	345.9	48	344.8	39	
$v_{31}$	475.4	9	306.9	7	417.3	27	410.8	26	
$v_{31}$	146.0	74	437.8	16	317.7	5	308.6	23	
$v_{32}$	173.4	7	141.8	22	290.3	6	294.7	8	
$\nu_{33}$	345.4	21	194.7	58	216.3	7	213.1	9	
$v_{34}$	213.8	1	210.9	6	148.0	14	134.7	13	
$\nu_{35}$	98.9	4	101.3	4	139.2	28	120.3	37	
<i>v</i> <sub>36</sub>	35.4	0	31.8	1	45.7	10	47.1	7	

Table B.10 Anharmonic vibrational frequencies (cm<sup>-1</sup>) and intensities (km mol<sup>-1</sup>) for  $\alpha$ -serine conformers 13 and 14, calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory.

	Ser-13				Ser-14			
Mode	MP2 B3LYP-D3BJ			-D3BJ	MP2 B3LYP-D3BJ			
	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>ν</b> / cm <sup>-1</sup>	Int.
$\nu_1$	3698.7	46	3653.4	40	3679.0	33	3625.3	26
$\nu_2$	3576.4	68	3536.7	53	3580.7	73	3540.7	60
$\nu_3$	3460.0	9	3413.1	7	3483.2	13	3441.3	13
$ u_4 $	3384.4	4	3364.8	3	3392.4	2	3367.5	2
$\nu_5$	3005.7	18	2935.9	22	3028.9	15	2962.3	19
$\nu_6$	2968.2	12	2895.1	18	3000.9	17	2958.3	16
$\nu_7$	2919.5	11	2874.2	9	2848.6	40	2777.6	30
$\nu_8$	1785.1	168	1766.6	213	1794.9	45	1783.8	158
$\nu_9$	1597.0	21	1663.7	5	1611.7	14	1593.5	24
$\nu_{10}$	1481.9	5	1465.6	7	1471.2	2	1456.4	2
$\nu_{11}$	1409.1	1	1401.5	0	1400.7	4	1381.4	2
$v_{12}$	1371.6	13	1355.8	0	1380.1	20	1367.9	6
$v_{13}$	1339.0	17	1320.0	7	1352.9	9	1340.5	3
$v_{15}$	1309.5	20	1290.3	15	1318.8	10	1303.8	3
$v_{16}$	1283.0	17	1275.1	26	1292.9	0	1285.9	1
$v_{17}$	1230.7	17	1218.8	12	1230.1	8	1222.5	6
$\nu_{18}$	1122.8	9	1143.0	26	1166.6	28	1157.8	8
$\nu_{19}$	1133.0	133	1104.7	143	1148.5	13	1129.2	16
$\nu_{20}$	1169.6	8	1125.5	5	1108.9	245	1090.0	231
$v_{21}$	1048.2	64	1031.2	72	1062.2	23	1032.2	44
$v_{22}$	1023.7	20	998.1	29	1012.6	44	995.8	66
$v_{23}$	910.0	64	884.1	1	930.8	10	901.1	21
$v_{24}$	879.6	195	819.7	125	865.8	5	851.0	4
$v_{25}$	828.3	14	809.0	42	789.2	120	720.4	20
$v_{26}$	748.0	25	736.2	27	713.3	54	699.6	151
$v_{27}$	640.9	112	634.9	102	663.1	19	658.1	18
$\nu_{28}$	560.5	29	556.6	35	532.7	57	528.4	43
$\nu_{29}$	524.6	13	518.3	21	492.5	4	491.4	11
$\nu_{30}$	482.7	4	475.8	4	426.2	9	421.5	9
$v_{31}$	375.6	4	362.3	2	361.5	5	364.8	4
$v_{31}$	155.5	25	149.6	25	390.5	16	357.5	21
$v_{32}$	299.3	5	342.7	7	143.5	38	126.8	33
$v_{33}$	276.6	34	244.1	6	246.0	63	258.5	60
$v_{34}$	186.7	131	194.0	90	202.9	1	205.8	6
$v_{35}$	113.7	2	58.4	23	130.7	4	122.4	4
<i>v</i> <sub>36</sub>	46.3	4	40.9	2	48.5	0	51.7	0

		Se	r-15				-	
Mode	MP2		B3LYP-D3BJ		MP2		B3LYP-D3BJ	
	<b>ν</b> / cm <sup>-1</sup>	Int.	<b>v</b> / cm <sup>-1</sup>	Int.	<b>v</b> / cm <sup>-1</sup>	Int.	<b>v</b> / cm <sup>-1</sup>	Int.
$\nu_1$	3696.9	46	3654.8	39				
$\nu_2$	3583.7	65	3538.3	46				
$\nu_3$	3441.2	9	3395.1	8				
$ u_4 $	3372.7	3	3346.4	2				
$\nu_5$	3005.2	20	2929.8	28				
$\nu_6$	2966.7	16	2894.2	13				
$\nu_7$	2918.4	9	2859.5	7				
$\nu_8$	1795.4	140	1782.4	100				
$\nu_9$	1605.2	22	1608.9	6				
$\nu_{10}$	1482.9	1	1467.9	6				
$\nu_{11}$	1412.6	1	1406.7	3				
$\nu_{12}$	1358.2	0	1360.0	0				
$\nu_{13}$	1373.8	9	1335.5	4				
$\nu_{15}$	1296.3	11	1270.5	1				
$\nu_{16}$	1277.3	1	1283.1	21				
$\nu_{17}$	1225.4	9	1219.6	9				
$\nu_{18}$	1170.8	2	1163.4	3				
$\nu_{19}$	1141.9	6	1119.5	8				
$\nu_{20}$	1101.8	211	1087.4	156				
$v_{21}$	1050.3	50	1030.9	50				
$v_{22}$	1024.7	16	1003.6	42				
$\nu_{23}$	902.7	118	894.1	4				
$\nu_{24}$	919.3	1	851.0	130				
$\nu_{25}$	834.0	13	817.9	11				
$v_{26}$	743.1	21	732.0	10				
$v_{27}$	638.2	19	626.4	31				
$v_{28}$	563.6	53	572.8	66				
$\nu_{29}$	508.8	13	500.4	21				
$v_{30}$	470.9	14	466.8	14				
$v_{31}$	349.6	47	352.7	31				
$v_{31}$	368.2	15	211.8	12				
$v_{32}$	148.7	32	366.2	24				
$v_{33}$	208.9	28	123.5	22				
$v_{34}$	199.3	90	178.5	98				
$\nu_{35}$	113.6	1	108.3	1				
$v_{36}$	60.9	1	55.9	1				

Table B.11 Anharmonic vibrational frequencies (cm<sup>-1</sup>) and intensities (km mol<sup>-1</sup>) for  $\alpha$ -serine conformer 15, calculated at the MP2/cc-pVTZ and B3LYP-D3BJ/def2-TZVPD levels of theory.