Heavy-Atom Structure of Alaninamide from Rotational Spectroscopy

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The rotational transitions of seven isotopomers of alaninamide, the amide derivative of alanine, were measured using a Fourier transform microwave spectrometer. Least-squares fitting and Kraitchman's method of isotopic substitution were used to determine the heavy-atom structure and indicate that the spectra can be assigned to a conformation with an intramolecular hydrogen bond from the amide to the amine. This conformation corresponds to the lowest energy ab initio structure, optimized at the MP2/6-31+G†† level. The experimental structure of alaninamide is also compared to the structures of the amino acids glycine and alanine.

Introduction

The conformations of simple amino acids have been the subject of increasing study due to their potential relationship to the structures of larger peptides. Microwave spectroscopy, electron diffraction, and matrix isolation infrared spectroscopy have shown that multiple conformations of an amino acid may be detected experimentally; three different conformations of glycine have been identified experimentally to date.[1−7] The lowest energy structure, conformer **I**, has an intramolecular hydrogen bond from the amine to the carboxyl oxygen, while a second low-energy structure, conformer **II**, has a hydrogen bond from the carboxylic acid to the amino nitrogen. Because of its larger dipole moment, the rotational spectrum of glycine conformer **II** was reported[1] before the conformer **I** spectrum was found.[2] Hartree−Fock (4-31G) calculations correctly predicted conformer **I** to be lower in energy than conformer **II** and later aided in the identification of its spectrum.[8,9] Recently, the Kraitchman substitution coordinates for the heavy atoms of both conformers **I** and **II** have been determined from the millimeter wave spectra of glycine isotopes.[3] High-resolution microwave spectra have also resolved the nuclear quadrupole hyperfine structure and enabled more precise measurements of the μ_a and μ_b dipole components.[4]

Gas-phase electron diffraction experiments on glycine have also shown that conformer **I** is the lowest energy structure.[5] Although the heavy-atom structure and C − C bond torsional potential energy function of conformer **I** were obtained from the electron diffraction pattern, no structural evidence for the other conformers could be deduced from these experiments. Recent matrix-isolation infrared spectra of glycine include features from three different conformers[6,7] (conformer **III** is a low-energy conformation with a bifurcated hydrogen bond from the amine to the hydroxyl oxygen). However, the transitions assigned to conformer **III** disappear rapidly as the matrix temperature is raised above 13 K, behavior which was attributed to a low potential energy barrier separating conformers **III** and **I**. Extensive theoretical studies[8−15] have identified up to 13 likely glycine conformers.[10]

High-level ab initio studies have also found 13 minima on the conformational potential energy surface of alanine.[16,17] The energy order of the alanine conformers matches the order found for glycine,[17] indicating that the additional methyl group has only a small effect on alanine's conformational preferences. An electron diffraction study characterized the lowest energy conformation,[18] and rotational spectra have been recorded for two low energy conformations, including the lowest energy conformer.[19] The spectroscopic experiments also provided a comparison of the dipole moment projections and ^{14}N-nuclear quadrupole coupling constants to HF/6-31G** theoretical models. Subsequent matrix infrared experiments detected the same conformations by shifts of the OH and OD stretching vibrations.[20] These two alanine conformations are analogous to glycine conformers **I** and **II** described above.

We have found that the amide derivatives of amino acids are easier to vaporize than the parent amino acids; amide derivatives may also serve as simple models for N-terminal amino acids in peptides. In a previous study, we recorded the microwave spectra of prolinamide[21] by heating the sample to 150 °C (melting point = 96 °C), far below the melting point of proline (228 °C). Spectroscopic features from only one conformation were found; the experimental moments of inertia and dipole moment were consistent with a conformation containing an intramolecular hydrogen bond from the amide to the amine ($\Psi = 0°$, corresponding to eclipsing nitrogens about the $C^{\alpha}-C'$ bond). In this paper we present the microwave spectrum and structure of alaninamide for comparison to the well-characterized glycine and alanine conformations.

Experimental Section

Rotational spectra were recorded for seven isotopomers of alaninamide using a Balle−Flygare[22] type Fourier transform microwave spectrometer (5−18 GHz) described in detail elsewhere.[23] The spectrometer consists of two 36 cm diameter aluminum mirrors. One of the mirrors is movable so that the cavity can be tuned to the desired frequency; the other mirror is fixed. Microwave radiation, generated by a Hewlett-Packard 83711B synthesized frequency generator, is coupled into the cavity by an L-shaped antenna; molecular emission is detected by a similar antenna on the opposite mirror and frequency reduced by a heterodyne circuit. The molecular signal is then digitized using a Keithley-MetraByte DAS-4101 data acquisition board in a personal computer. Injection of the sample into the cavity is accomplished by a heated nozzle oriented perpendicular

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TABLE 1: Frequencies (MHz) of the Assigned Nuclear Quadrupole Hyperfine Transitions of Alaninamide

J′ K′$_p$ K′$_o$ - J″ K″$_p$ K″$_o$	F′, I′ - F″, I″	ν_{obs}	$\Delta\nu$/kHz	J′ K′$_p$ K′$_o$ - J″ K″$_p$ K″$_o$	F′, I′ - F″, I″	ν_{obs}	$\Delta\nu$/kHz
1 0 1 - 0 0 0[a]		5411.853	−0.4	2 0 2 - 1 0 1[a]		10604.022	−2.2
	0, 1 - 1, 1	5412.613	13.0		1, 1 - 1, 1	10604.866	−3.2
	2, 2 - 2, 2	5412.378	−0.3		2, 2 - 1, 0	10604.380	−10.0
	1, 0 - 0, 0	5412.303	−8.1		3, 1 - 2, 1	10604.086	4.9
	1, 0 - 2, 2	5412.303	−8.1		2, 1 - 1, 1	10603.919	−2.9
	2, 1 - 1, 1	5411.933	7.3		4, 2 - 3, 2	10603.897	−4.1
	3, 2 - 2, 2	5411.709	4.9		1, 1 - 0, 1	10603.758	4.7
	1, 1 - 1, 1	5411.484	0.0		2, 1 - 2, 1	10603.480	−0.2
	1, 2 - 0, 0	5410.865	−4.3		1, 2 - 2, 2	10603.013	−7.1
	1, 2 - 2, 2	5410.865	−4.3		2, 0 - 2, 2	10602.882	10.5
					0, 2 - 1, 0	10602.625	7.5
1 1 1 - 0 0 0[a]		7229.183	2.3				
	1, 0 - 0, 0	7229.370	3.1	2 1 1 - 1 1 0[a]		11641.034	−1.2
	1, 0 - 2, 2	7229.370	3.1		2, 0 - 1, 0	11641.866	−6.3
	2, 1 - 1, 1	7229.207	−6.3		2, 2 - 1, 0	11641.410	−3.0
	3, 2 - 2, 2	7229.125	1.9		3, 1 - 2, 1	11641.087	−7.4
	1, 1 - 1, 1	7229.037	4.2		4, 2 - 3, 2	11640.919	8.3
	1, 2 - 0, 0	7228.786	−3.0		2, 1 - 1, 1	11640.680	16.5
	1, 2 - 2, 2	7228.786	−3.0		1, 1 - 1, 1	11640.367	4.3
					2, 0 - 1, 2	11639.853	−2.3
2 2 1 - 2 1 2[a]		7904.016	0.6		1, 2 - 1, 2	11639.798	−10.2
	2, 0 - 2, 0	7905.208	6.8				
	2, 1 - 2, 1	7904.911	4.0	2 1 2 - 1 0 1[a]		11823.672	−0.8
	3, 1 - 3, 1	7903.766	−1.5		3, 2 - 3, 2	11824.420	−2.6
	4, 2 - 3, 2	7903.629	0.7		1, 2 - 1, 2	11824.131	1.2
	2, 2 - 3, 2	7902.770	5.6		2, 2 - 1, 0	11824.131	4.6
	3, 2 - 2, 2	7902.669	−4.2		3, 2 - 2, 2	11823.741	−7.4
	2, 2 - 2, 2	7902.442	−11.5		3, 1 - 2, 1	11823.741	−5.2
					4, 2 - 3, 2	11823.522	0.0
2 0 2 - 1 1 1[a]		8786.700	2.7		2, 1 - 1, 1	11823.522	1.8
	3, 2 - 3, 2	8787.298	-0.8		2, 1 - 2, 1	11823.086	7.5
	3, 2 - 2, 2	8787.042	6.8				
	1, 1 - 0, 1	8786.880	3.2	3 1 3 - 2 1 2[a]		14886.573	3.4
	3, 1 - 2, 1	8786.813	11.0		3, 2 - 2, 2	14886.866	0.5
	2, 1 - 1, 1	8786.384	3.2		4, 2 - 3, 2	14886.609	−11.9
	2, 1 - 2, 1	8786.194	−6.3		3, 1 - 2, 1	14886.452	−0.9
	1, 2 - 1, 0	8786.026	−13.2		2, 2 - 2, 2	14885.406	0.9
	1, 2 - 2, 2	8786.016	3.7		3, 0 - 3, 2	14885.238	4.3
	2, 0 - 1, 0	8785.888	−2.6				
	2, 0 - 2, 2	8785.865	1.4	3 0 3 - 2 0 2[a]		15444.456	−3.0
					3, 2 - 2, 2	15444.742	5.2
2 1 2 - 1 1 1[a]		10006.346	0.0		4, 1 - 3, 1	15444.503	−12.0
	3, 2 - 2, 2	10006.730	−6.4		5, 2 - 4, 2	15444.339	6.8
	1, 1 - 0, 1	10006.574	3.0				
	3, 1 - 2, 1	10006.464	1.8				
	4, 2 - 3, 2	10006.102	−4.5				
	2, 0 - 1, 2	10006.053	3.6				
	2, 1 - 1, 1	10005.983	8.1				
	2, 1 - 2, 1	10005.786	−8.4				
	2, 0 - 1, 0	10005.469	−2.6				
	0, 2 - 1, 0	10005.120	5.3				

[a] The first entry is the unsplit center frequency calculated from fitting the ^{14}N quadrupole hyperfine transitions.

to the microwave cavity and resulting in rotational line widths of 30 kHz (full width at half-maximum), with line centers accurate to ±4 kHz.

L-Alaninamide, liberated from the hydrochloride salt with 1 M NaOH, was incorporated into a supersonic expansion by heating to 90 °C. The backing pressure of the argon carrier gas was typically 1.5 atm. The isotopically labeled species were prepared from isotopomers of L-alanine following the same four-step procedure described for prolinamide.[21] Briefly, these reactions protect the amine, activate the carbonyl, form the amide, and deprotect the amine. The products of intermediate steps were characterized by melting points and FTIR; a sample of the most abundant isotopomer of alaninamide, prepared in this way, was also characterized by comparison of the rotational spectrum to that from the commercially available material. ^{13}C- and ^{15}N-labeled alanine and $^{15}NH_4Cl$ were obtained from Cambridge Isotope Labs.

Results

Six *a*-type and four *b*-type rotational transitions were measured for the most abundant isotopic species (Table 1). Because of the two ^{14}N nuclei, each rotational transition was split into many nuclear quadrupole hyperfine components, generally spanning a 1.5 MHz range. These components were then fit to the quadrupole coupling constants $\chi_{aa}(N^1)$, $\chi_{bb}(N^1)$, $\chi_{aa}(N^2)$, and $\chi_{bb}(N^2)$ (Table 2; see Figure 1 for atom labels), yielding the frequencies of the unsplit rotational transitions. $(\nu_{obs} - \nu_{calc})_{rms} = 6.4$ kHz for the 76 hyperfine components. The rotational and centrifugal distortion constants derived from fitting the center frequencies to the Watson S-reduction Hamiltonian are presented in Table 2; $(\nu_{obs} - \nu_{calc})_{rms} = 2.0$ kHz for the fit. These 10 rotational transitions all arise from the same conformation of alaninamide; despite extensive searching, no

TABLE 2: Spectroscopic Constants of Alaninamide Isotopic Species

	alaninamide	$^{15}N^1$-alaninamide	$^{15}N^2$-alaninamide	$^{15}N^1$,$^{15}N^2$-alaninamide	$^{13}C'$,$^{15}N^2$-alaninamide	$^{13}C^\alpha$,$^{15}N^2$-alaninamide	$^{13}C^\beta$,$^{15}N^2$-alaninamide
A/MHz	4931.929(1)	4878.362(4)	4857.249(4)	4803.723(2)	4856.951(3)	4847.923(1)	4775.957(2)
B/MHz	3114.6022(8)	3072.733(2)	3086.550(3)	3045.702(2)	3075.483(2)	3074.041(1)	3047.9189(8)
C/MHz	2297.2573(8)	2264.864(3)	2271.780(3)	2240.033(2)	2265.949(2)	2266.253(1)	2240.336(1)
D_J/kHz	0.71(4)	0.7(1)	0.7(2)	0.76(9)	0.78(9)	0.71[a]	0.71(4)
N[b]	10	9	10	10	9	4	9
$\chi_{aa}(N^1)$	1.368(4)		1.288(4)		1.284(3)	1.27(2)	1.220(2)
$\chi_{bb}(N^1)$	0.606(5)		0.630(6)		0.626(4)	0.64(2)	0.789(3)
$\chi_{aa}(N^2)$	1.618(3)	1.640(4)					
$\chi_{bb}(N^2)$	0.598(5)	0.522(5)					

[a] D_J fixed to 0.71 kHz. [b] Number of center frequencies included in the fit.

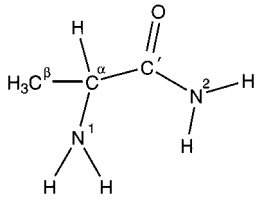

Figure 1. Molecular structure and atomic labels of alaninamide.

transitions were found which could be assigned to a second conformation.

Rotational transitions were also measured for each of the six isotopically labeled species: $^{15}N^1$-alaninamide, $^{15}N^2$-alaninamide, $^{15}N^1$,$^{15}N^2$-alaninamide, $^{13}C'$,$^{15}N^2$-alaninamide, $^{13}C^\alpha$,$^{15}N^2$-alaninamide, and $^{13}C^\beta$,$^{15}N^2$-alaninamide. Although the spectra of the single ^{15}N-substituted species exhibited nuclear quadrupole hyperfine structure, the splitting patterns were less extensive and easier to assign. For this reason, the ^{13}C isotopes also have ^{15}N-substitution at the amide position. The spectroscopic constants for these species can be found in Table 2, and the transition frequencies are available in the Supporting Information.

Discussion

We used GAUSSIAN94[24] to model the conformations of alaninamide. Three conformational minima were found from geometry optimizations using the complete basis set methods of Petersson et al.[25] at the MP2/6-31+G†† level; these structures are shown in Figure 2. The lowest energy structure, conformer **1**, has an intramolecular hydrogen bond from the amide to the amine and is similar to conformer **II** of glycine. Conformer **2** is 6.56 kJ mol^{-1} higher in energy than conformer **1** (Table 3); it contains an amine-to-carbonyl hydrogen bond. Conformer **2** is somewhat similar to glycine conformer **I**, although the hydrogen bond in alaninamide conformer **2** is not perfectly bifurcated. The third alaninamide conformer is 15.23 kJ mol^{-1} above the minimum and has just one amino hydrogen directed toward the carbonyl oxygen; this structure is similar to glycine conformer **IVn**.[10] All three alaninamide conformers have significantly different heavy-atom structures. The principal-axis coordinates of the three conformers are available as Supporting Information.

Table 3 also reports the root-mean-square averages of the differences between observed and calculated moments of inertia: ΔI_{rms} where $\Delta I = I_x(\text{obs}) - I_x(\text{calcd})$ and x = *a*, *b*, and *c* for each isotopomer. Conformer **1** best reproduces the spectroscopic data from the seven isotopomers. A least-squares fit of the heavy-atom structure to the rotational constants was performed using the program STRFITQ[26] and using each of the ab initio conformations as starting structures. For each fit, 12 internal coordinates describing the positions of the heavy atoms were adjusted while internal coordinates describing the hydrogen positions were fixed to the ab initio values (N^1−H: 1.017 Å; N^2−H: 1.009 Å; C^α−H: 1.102 Å; and C^β−H: 1.095

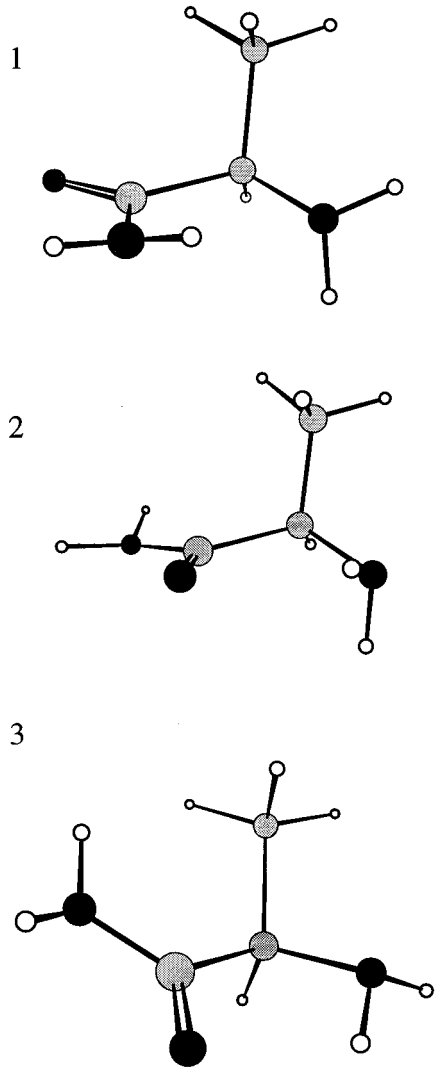

Figure 2. Ab initio model conformations of alaninamide. Conformer **1** was found to be the lowest energy structure at the MP2/6-31+G††level; conformers **2** and **3** are 6.56 and 15.23 kJ mol^{-1} higher in energy than conformer **1**.

TABLE 3: Ab Initio Conformers of Alaninamide

	E/hartree	ΔE/kJ mol^{-1} [a]	ΔI_{rms}/amu Å^2
conformer **1**	−302.0526	0	1.45
conformer **2**	−302.0501	6.56	6.49
conformer **3**	−302.0468	15.23	13.49

[a] ΔE is relative to conformer **1**.

TABLE 4: Atomic Coordinates (Å) of the Heavy Atoms of Alaninamide in the Principal Inertial Axis System of $^{15}N^2$-Alaninamide Determined from Kraitchman's Equations and Least-Squares Fitting of the Moments of Inertia

	Kraitchman	least squares
N^1		
a	±1.444	1.447
b	±1.053	−1.056
c	±0.326	0.316
C^α		
a	±0.712	0.720
b	±0.197	0.234
c	±0.405	0.392
C^β		
a	±1.297	1.300
b	±1.205	1.208
c	±0.616	−0.620
C′		
a	±0.763	−0.765
b	±0.072i	−0.006
c	±0.108	0.129
N^2		
a	±1.109	−1.096
b	±1.133	−1.120
c	±0.535	−0.519

TABLE 5: Principal Axis Atomic Coordinates (Å) of the Best-Fit Structure of Alaninamide

	a	*b*	*c*
N^1	1.455	−1.042	0.307
$H(N^1)$	2.450	−0.837	0.344
$H(N^1)$	1.258	−1.604	1.131
C^α	0.701	0.232	0.392
$H(C^\alpha)$	0.719	0.695	1.392
C^β	1.266	1.228	−0.607
$H(C^\beta)$	0.664	2.141	−0.599
$H(C^\beta)$	2.301	1.487	−0.357
$H(C^\beta)$	1.248	0.796	−1.614
C′	−0.778	−0.036	0.119
O	−1.618	0.864	0.377
N^2	−1.083	−1.150	−0.542
$H(N^2)$	−0.319	−1.723	−0.870
$H(N^2)$	−1.982	−1.187	−0.996

Å; bond angles involving H can be determined from the data in Supplementary Tables 7−9). The best fit structure of conformer **1** reproduces the experimental moments of inertia with $\Delta I_{rms} = 0.0068$ amu Å^2; the fits of conformers **2** and **3** did not converge. The experimental spectra are therefore assigned to conformer **1**.

The substitution coordinates of the heavy atoms, excluding oxygen, were also calculated from Kraitchman's equations for single isotopic substitution.[27,28] Since all ^{13}C isotopic species were also labeled at the amide nitrogen, these calculations were made with reference to $^{15}N^2$-alaninamide and are in the principal inertial axis system of this isotopic species. The substitution coordinates and the atomic coordinates resulting from the fitting procedure (also in the $^{15}N^2$-alaninamide principal axis frame) are compared in Table 4 and are in excellent agreement. Not surprisingly, the largest differences between the substitution and least-squares-fit coordinates occur for the smallest values, where the effects of zero-point vibrations are greater than for the other Kraitchman coordinates. The very small value of the C′ *b* coordinate is also heavily perturbed by zero-point vibrations and results in an imaginary number in the Kraitchman analysis. Table 5 provides all of the atomic coordinates of the least-squares-fit structure in the principal inertial axis system of the most abundant isotopic species.

The bond lengths and angles in alaninamide (Table 6) are comparable to corresponding parameters of formamide and

TABLE 6: Heavy-Atom Bond Lengths (angstroms), Angles (Degrees), and Torsional Angles (Degrees) from the Least-Squares Fit and the ab Initio Model of Alaninamide

	least squares	ab initio
N^1-C^α	1.482 (6)	1.468
$C^\alpha-C'$	1.528 (8)	1.534
$C^\alpha-C^\beta$	1.520 (5)	1.529
C′−O	1.258 (30)	1.223
$C'-N^2$	1.331 (36)	1.364
$N^1-C^\alpha-C^\beta$	109.7 (2)	109.5
$N^1-C^\alpha-C'$	109.3 (16)	111.4
$C^\alpha-C'-O$	119.0 (26)	121.2
$C^\alpha-C'-N^2$	117.2 (18)	114.2
$N^1-C^\alpha-C'-N^2$	21.0	13.6
$N^1-C^\alpha-C'-O$	−167.4	−166.9
$C^\beta-C^\alpha-C'-N^2$	−100.0	−106.7

conformer **II** of glycine. The N^1-C^α and $C'-C^\alpha$ bonds are 1.459 and 1.545 Å in glycine[3] and the C′−O and $C'-N^2$ bonds are 1.219 and 1.352 Å in formamide.[29] The heavy-atom bond lengths and angles also fall within 3% of their values in the initial ab initio model structure (also in Table 6). The least-squares-fit structure is an average molecular structure at the zero-point vibrational level (an r_0 structure), while the ab initio structure corresponds to the equilibrium geometry (an r_e structure). Thus, much of the difference between the two structures in Table 6 can be ascribed to vibrational averaging in the experimental structure. We used Costain's rule[28] to estimate the vibrational contribution to the experimental uncertainties. The uncertainties are less than 3° for the angles and less than 0.01 Å for the N^1-C^α, $C^\alpha-C'$, and $C^\alpha-C^\beta$ bond lengths. The larger uncertainties (0.030 and 0.036 Å) for the C′−O and $C'-N^2$ bond lengths arise from the small *b*-coordinate of C′. We also estimate that the uncertainties in the torsional angles are approximately 5°, making the significance of the greater $N^1-C^\alpha-C'-N^2$ twist angle of the experimental structure somewhat questionable.

Conformer 1 of alaninamide is stabilized by an intramolecular hydrogen bond from the amide to the amine. The 2.678 Å N−N distance of this hydrogen bond is comparable to the O−N heavy atom separation in the intramolecular hydrogen bonds of glycine[10] and alanine,[17] calculated (MP2) to be 2.614 and 2.591 Å, respectively. We also calculated the hydrogen bond length and angle for alaninamide using the best-fit heavy-atom structure (which relies on the ab initio values of the hydrogen internal coordinates). The distance from the amide hydrogen to the amino nitrogen is found to be 2.235 Å, and the N−H−N bond angle is 104.9°. These structural parameters are consistent with previously reported intramolecular hydrogen bonds.[30]

It is interesting that the energy ordering of the stable conformations of alaninamide differs from the ordering for glycine and alanine. The lowest energy conformer of alaninamide is most similar to conformer **II**, a higher energy conformation, of glycine and alanine. The relative stabilities of the conformations depend, to a large extent, on the intramolecular hydrogen bonds; amide derivatization will have a large effect on their relative strengths. For example, the trans configurations of carboxylic acids are less stable than the cis configurations (24 kJ mol^{-1} for formic acid[11]). Since glycine conformer **II** (hydrogen bond from the acid to the amine) has the acid group trans to the carbonyl, the cis−trans energy difference is *one* component of the energy difference between glycine conformers **I** and **II**. Alaninamide, however, has both cis and trans hydrogen atoms, so a trans hydrogen is available to participate in an intramolecular hydrogen bond to the amine without overcoming the cis−trans energy difference.

Conclusions

We have assigned rotational transitions of seven isotopically labeled species of alaninamide, the amide derivative of alanine. The atomic coordinates of the heavy atoms were determined from Kraitchman's equations for single isotopic substitution and compared to the atomic coordinates of the structure that best fits the moments of inertia. The Kraitchman and best fit structures describe a conformation with an intramolecular hydrogen bond from the amide to the amine. The best-fit structure was also found to be the lowest energy conformation by optimizations at the MP2/6-31+G†† level.

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Supporting Information Available: Tables of transition frequencies for the isotopic species of alaninamide and tables of atomic coordinates of the ab initio structures of conformers 1−3. Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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