Anharmonic Vibrational Spectroscopy of Glycine: Testing of ab Initio and Empirical Potentials

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The second-order Møller−Plesset ab initio electronic structure method is used to compute points on the potential energy surface of glycine. Some 50 000 points are computed, covering the spectroscopically relevant regions, in the vicinity of the equilibrium structures of the three lowest-lying conformers of glycine. The vibrational states and spectroscopy are computed directly from the potential surface points using the correlation corrected vibrational self-consistent field (CC-VSCF) method, and the results are compared with experiment. Anharmonic effects and couplings between different vibrational modes that are included in the treatment are essential for satisfactory accuracy. The following are found: (1) The spectroscopic predictions from the ab initio potential are in very good accord with matrix experiments. (2) Theory agrees even more closely with spectroscopic data for glycine in He droplets, where environmental effects are much weaker than in the matrix. This suggests that errors in the ab initio potential are smaller than rare-gas matrix effects. (3) The accuracy of the ab initio potential is, by this spectroscopic test, much superior to that of OPLS-AA, a state-of-the-art empirical potential. The relative failure of the empirical potential is due to its inability to describe details of the hydrogen-bonded interactions, and is most critical in one of the glycine conformers where such interactions play an especially important role.

I. Introduction

Ab initio electronic structure methods have been used extensively in recent years to study small biological molecules. The main features addressed by these methods are structure and relative energetics of different conformers, as well as their harmonic vibrational frequencies. Theoretically obtained structure and vibrational spectra play a crucial role in the interpretation of the experimentally observed data. Practically all experimental studies of IR spectra of small biomolecules, published in recent years, are complemented by theoretical calculations to help the interpretation of results.

The main theoretical tool used for this purpose is harmonic vibrational analysis, routinely available at the present time from all electronic structure packages. However, harmonic vibrational frequencies can be spectroscopically very inaccurate, with deviations from experimental frequencies up to 200−300 cm^{-1} for the highest stretching vibrations. The anharmonic effects in the floppy biological molecules are often particularly large. In "microsolvation" systems, e.g., complexes of biological molecules with H_2O, the anharmonic effects are even greater. The deficiencies of the harmonic approximation are usually corrected by scaling the harmonic frequencies. This technique, though practical, is inherently empirical and often fails to predict correct anharmonicities for floppy biological systems, especially when strong hydrogen bonding effects are present. Another issue is that the anharmonic properties of the potential surfaces are of great interest. The experimental spectroscopic data carries important information on this issue, but it is necessary to use anharmonic theoretical calculations for interpretation of the experimental data.

Recently, we have developed an algorithm that combines anharmonic vibrational spectroscopy with direct calculation of ab initio potentials.[1] The method accounts for anharmonicities and couplings between vibrational modes using the correlation corrected vibrational self-consistent field (CC-VSCF) approach,[2,3] and therefore provides a superior alternative to the existing techniques based on scaling the harmonic vibrational frequencies. This method was applied to a number of hydrogen-bonded systems[4] using the potentials obtained at the MP2 level of ab initio theory and was shown to provide fairly accurate anharmonic frequencies, with typical deviations from experimental values of the order of 30−70 cm^{-1}, depending on the quality of the basis set used for obtaining ab initio potential points.

In this paper, we apply the direct ab initio CC-VSCF method to obtain anharmonic vibrational spectra for the three lowest conformers of the simplest amino acid glycine. Vibrational spectra of glycine molecule have been studied experimentally recently in Ar matrices[5] and in helium clusters.[6] We compare the calculated ab initio anharmonic spectra with experimental data and confirm the assignments for the highest stretching vibrational frequencies of the three glycine conformers. We analyze the intramolecular hydrogen bonding interactions in these conformers and their effects on the vibrational spectra. The paper has several objectives. First, we provide a quantitative test, by the comparison with experimental frequencies, of the accuracy of the ab initio potential surface. Indeed, the agreement found is very good, and is very encouraging for using this level of ab initio electronic structure method to generate anharmonic potential surfaces for small biological molecules. Second, we compare, again using agreement with spectroscopy experiments

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as the standard, the quality of the ab initio potential with that of a state-of-the-art empirical force field (OPLS-AA). The relative accuracy of these potentials is of great importance, since empirical force fields are currently widely used in the modeling of biological molecules. We shall find the ab initio potential much superior. Finally, we pursue an analysis of the anharmonic couplings between the modes, e.g., which pairs are mutually strongly coupled. Very interesting properties are found, and again there seems to be a major difference between the empirical and the ab initio potentials. There may be interesting consequences for intramolecular vibrational energy transfer between different modes, which are due to anharmonic coupling.

II. Methodology

The glycine molecule is one of the smallest representatives of biologically important systems. Despite its relatively small size, the conformational structure of glycine is very rich and has many important features common to all amino acids. At least eight neutral minimum-energy conformers of glycine have been identified in previous theoretical studies, which employed different levels of semiempirical, ab initio, and DFT electronic structure theories.[7−11] At the same time, only three conformers (predicted to have the lowest energies by theoretical calculations) were found experimentally in the gas phase,[12,13] and their vibrational spectra have been measured in Ar matrices[5] and in He clusters.[6] Previous theoretical studies have mostly addressed the issues of geometrical structure and relative energetics of glycine conformers, as well as their harmonic frequencies.[8,9] The structure of the transition states between the conformers and the kinetics of conformational interconversion have also been investigated.[7]

In the present study only the three lowest conformers of glycine are considered, but their potential energy surfaces are computed over substantial regions around the corresponding local minima, which is important for analysis of anharmonicities and for calculation of anharmonic vibrational spectra that can be compared with experiment. The level of ab initio theory used here for studying glycine potential energy surface is second-order Møller−Plesset perturbation theory (MP2)[14] with Dunning−Hay double-ζ + polarization (DZP) basis set.[15] It follows from previous ab initio studies, which used several levels of ab initio theory to investigate relative energetics of glycine conformers,[8,9] that the lowest level needed for good quantitative description of energetics is MP2 with a reasonably large basis set, and that using higher levels of theory (MP4, CCSD(T)) improves the relative energetics only very slightly. In this study, we test this level (MP2/DZP) of electronic structure theory not only for energetic differences of glycine conformers, but also for anharmonic parts of the potential energy surfaces. The calculated potential surfaces are used to obtain anharmonic vibrational spectra, and the comparison with experiment serves as the criterion of the quality of the computed potential energy surfaces.

The equilibrium geometries of the three lowest conformers of glycine are optimized using analytic gradients of the MP2/DZP energies. In the case of the conformer 3, the structure was optimized with the frozen C_s symmetry to obtain the lowest symmetric structure instead of the nonsymmetric local minimum. Second-derivative (Hessian) matrices were calculated numerically using double differencing.

After harmonic normal-mode analysis was performed, anharmonic vibrational frequencies were obtained using vibrational self-consistent field (VSCF) method and its correlation corrected (CC-VSCF) extension via second-order perturbation theory.[2] The calculations were performed using the combined ab initio/VSCF approach described in detail in previous papers[1,4] and implemented in the electronic structure package GAMESS.[16] This method employs a grid over a region of the space of normal coordinates, which covers the domain of nuclear configurations relevant to the vibrational states computed. The potential energy values are computed for these grid points.

The essence of the VSCF method is the separability approximation, which reduces the problem of solving the N-dimensional vibrational Schrödinger equation for the N-mode system to solving N single-mode VSCF equations of the form

$$\left[-\frac{1}{2}\frac{\partial^2}{\partial Q_j^{\,2}} + \bar{V}_j^{(n_j)}(Q_j)\right]\Psi_j^{(n_j)} = \epsilon_n \Psi_j^{(n_j)} \qquad (1)$$

where $\bar{V}_j^{(n_j)}(Q_j)$ is the effective VSCF potential for mode Q_j:

$$\bar{V}_j^{(n_j)}(Q_j) = \langle \prod_{l\neq j}^{N} \psi_l^{(n_l)}(Q_l) | V(Q_1,...,Q_N) | \prod_{l\neq j}^{N} \psi_l^{(n_l)}(Q_l) \rangle \qquad (2)$$

$V(Q_1, ..., Q_N)$ is the full potential of the system. The total vibrational state of the system in this approximation is given by

$$\Psi = \prod_{j}^{N} \psi^{(n_j)}{}_j(Q_j)$$

The above equations are solved self-consistently. The numerical pointwise collocation technique[17] is used in this study to solve the one-dimensional VSCF equations. The resulting VSCF solutions are further corrected for correlation effects between the vibrational modes using second-order perturbation theory (CC-VSCF).[2] Based on experience in previous applications, the CC-VSCF method provides a sufficient level of accuracy for our purpose in treating the vibrational states even in some very demanding cases.[2−4,18]

To simplify the numerical integration and to reduce the number of points at which the ab initio potential energy needs to be evaluated, the following approximation is used: the potential of the system $V(Q_1,...,Q_N)$ is represented by the sum of separable (single-mode) terms and pair coupling terms, neglecting triple and higher body mode−mode interactions (pairwise approximation):

$$V(Q_1,...,Q_N) = \sum_{j}^{N} V_j^{\mathrm{diag}}(Q_j) + \sum_{i}\sum_{i<j} V_{ij}^{\mathrm{coup}}(Q_i,Q_j) \qquad (3)$$

"Diagonal" (single-mode) terms $V_i^{\mathrm{diag}}(Q_i) = V(0,...,Q_i,...,0)$ and the pairwise mode−mode coupling terms $V_{ij}^{\mathrm{coup}}(Q_i,Q_j) = V(0,...,Q_i,...,Q_j,...,0) - V^{\mathrm{diag}}(Q_i) - V^{\mathrm{diag}}(Q_j)$ are calculated directly from the ab initio program on eight point grids along each normal coordinate, and on 8×8 square grids for each pair of normal coordinates. This requires computation of 17 856 ab initio potential energy points for each conformer of glycine. Obtaining the potential points along each single normal mode allows us to account for one-dimensional anharmonicities, while the square grids of points for each pair of normal modes is required in order to account for coupling effects between the modes. The calculated ab initio potentials are interpolated into 16 and 16×16 point grids using polynomial interpolation. The resulting grids of potential points are used to form one-dimensional effective VSCF potentials (2). This interpolation

scheme was shown to work well for several molecules and hydrogen-bonded clusters in our previous study.[4]

The validity of the pairwise approximation was tested previously and shown to work reasonably well for water clusters and other hydrogen-bonded systems.[1,2,4] Addition of three-mode coupling terms in eq 2 for the effective VSCF potential in test cases of three- and four-atomic molecules (e.g., H_2O, $Cl^-(H_2O)$) showed that the three-body coupling effects, though not negligible, are far less important than the pair coupling contributions, and are smaller than the errors due to the inaccuracy of the potential energy surfaces (e.g., the size of the basis set used in ab initio calculations). Although the quality of the pairwise approximation has not been tested for biological molecules, we expect this approximation to work even better for such molecules than for the hydrogen-bonded complexes of water, since they are more rigid.

Note that the accuracy of the VSCF approximation itself in hydrogen-bonded systems was tested primarily for higher frequency modes. The situation may be different for low-frequency torsional modes where not only the pairwise approximation, but also more fundamental approximations (e.g., the separability (VSCF) approximation and the use of normal-mode coordinates), may sometimes fail in the case of very floppy systems. Again, we expect the VSCF approach to work more reliably for biological molecules than for much floppier hydrogen-bonded clusters studied before.

In addition to anharmonic vibrational frequencies, the anharmonic IR intensities are calculated using dipole moments estimated in the process of ab initio calculations:

$$I_i = \frac{8\pi^3 N_A}{3hc}\omega_i|\langle\psi_i^{(0)}(Q_i)|\vec{\mu}(Q_i)|\psi_i^{(1)}(Q_i)\rangle|^2 \qquad (4)$$

where ω_i is the VSCF fundamental vibrational frequency for the normal mode i; $\psi_i^{(0)}$ and $\psi_i^{(1)}$ are VSCF wave functions for the ground and the first excited vibrational states. Although VSCF wave functions are not exactly orthogonal, tests show that the errors due to this issue are almost negligible and practically do not affect the calculated intensities.

III. Results and Discussion

III.1. Geometry of Glycine Conformers. Geometrical parameters and relative energies of the three lowest glycine conformers are shown in Figure 1. The conformational structure and energetics of glycine have been studied extensively previously using different levels of ab initio[7−9] and DFT[10,11] theory. The relative energies of conformers 2 and 3 with respect to the lowest conformer 1, obtained at the level used in this paper (MP2/DZP) are 0.63 and 1.40 kcal/mol (1.02 and 1.48 kcal/mol when harmonic zero point energy corrections are included), which is in good agreement with higher level CCSD(T) ab initio calculations.[8,9] A very important and interesting structural feature that distinguishes different conformers of glycine is intramolecular hydrogen bonding. Conformers 1 and 3 have very weak hydrogen bonds between NH_2 hydrogens and C═O or C−OH oxygen atoms. Conformer 2 has a much stronger H-bond between the hydrogen of the O−H group and the nitrogen atom of the NH_2 group (see Figure 1). These hydrogen bonding intramolecular interactions are an important feature of the potential energy surface of glycine and affect the geometry and vibrational spectroscopy of the glycine conformers. The correct theoretical description of vibrational frequencies is especially sensitive to the quality of the potential energy surfaces and requires accurate methods that include electron correlation and properly describe the effects of hydrogen bonding.

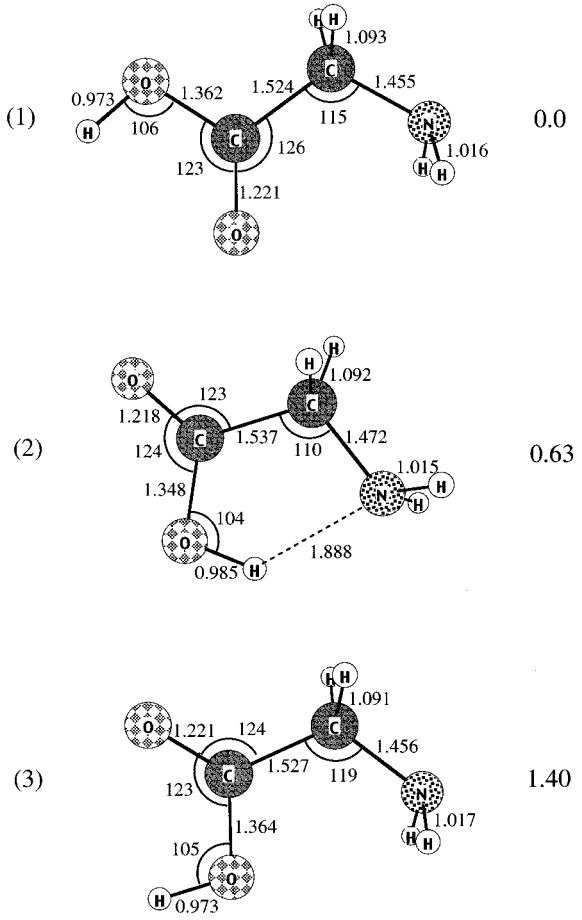

Figure 1. Equilibrium structures (Å, deg) and relative energies (kcal/mol) of the lowest energy conformers of glycine (MP2/DZP level of ab initio theory).

III.2. Spectroscopy Calculations for ab Initio Potential and Comparison with Experiment. The results of ab initio vibrational spectroscopy calculations for glycine conformers 1−3 are shown in Tables 1−3, respectively. MP2/DZP method was used to obtain both harmonic vibrational frequencies (shown in the first column of the tables) and the potential energy points needed for anharmonic corrections (VSCF and correlation corrected VSCF presented in the second and third columns, respectively). Also shown are experimental frequencies from the literature (measured in Ar matrix[5] and in He droplets[6]). Finally, calculated IR intensities as well as the assignments for the highest frequency vibrations are presented (last column).

It can be seen from Tables 1−3 that the harmonic approximation overestimates vibrational frequencies in most cases. This error is especially large for the highest frequency stretching vibrations, where it is of the order of 200−250 cm^{-1}. Anharmonic and mode−mode coupling corrections calculated using VSCF and CC-VSCF approximations improve the agreement with experiment significantly, bringing the average error down to about 25−30 cm^{-1}. However, part of the difference between our calculated frequencies and the experimental ones measured in the Ar matrix can probably be attributed to the matrix effects. This conclusion is supported by the much closer agreement of the calculated O−H stretching frequencies with the experimental data measured in He droplets, where the perturbation due to the matrix environment is much smaller. The differences between the calculated O−H stretching frequencies and the ones measured in He are 13 and 5 cm^{-1} for conformers 1 and 2,

TABLE 1: Vibrational Frequencies and IR Intensities for Glycine Conformer 1

mode	vibrational frequencies, cm^{-1} harmonic	VSCF	CC-VSCF	expt[a]	expt[b]	intensity, km/mol	description
1	3829	3562	3598	3560	3585	109	OH stretch
2	3688	3424	3382	3410		5	NH stretch asym
3	3590	3401	3343			3	NH stretch sym
4	3213	3018	2986			17	CH stretch asym
5	3148	3016	2959	2958		22	CH stretch sym
6	1836	1807	1805	1779		414	C═O stretch
7	1702	1675	1669	1630		23	HNH bend
8	1495	1473	1473	1429		13	HCH bend
9	1443	1414	1410	1373		30	
10	1410	1383	1377			0	
11	1327	1299	1290			23	
12	1205	1191	1185			1	
13	1195	1176	1167	1136		99	
14	1155	1134	1122	1101		232	
15	975	986	970	907		184	
16	937	949	943	883		3	
17	852	855	847	801		60	
18	665	697	613	619		143	
19	636	636	633			16	
20	516	555	514	500		23	
21	467	466	463	463		38	
22	259	272	270			11	
23	240	414	352			54	
24	58	177	143			4	

[a] Experimental data obtained in Ar matrix.[5] [b] Experimental O−H stretch obtained in He cluster.[6]

TABLE 2: Vibrational Frequencies and IR Intensities for Glycine Conformer 2

mode	vibrational frequencies, cm^{-1} harmonic	VSCF	CC-VSCF	expt[a]	expt[b]	intensity, km/mol	description
1	3715	3452	3428	3410		16	NH stretch asym
2	3612	3428	3360			2	NH stretch sym
3	3559	3241	3270	3200	3275	320	OH stretch
4	3225	3024	2989			15	CH stretch asym
5	3152	3016	2958	2958		18	CH stretch sym
6	1860	1828	1824	1790		472	C═O stretch
7	1692	1658	1653	1622		52	HNH bend
8	1507	1485	1483	1429		8	HCH bend
9	1446	1410	1399	1390		483	COH bend/CO s/CC s
10	1396	1369	1363			26	
11	1347	1322	1317			13	
12	1256	1227	1219	1210		7	
13	1186	1173	1166	1130		4	
14	1101	1077	1073			14	
15	982	988	976	911		119	
16	924	939	926	880		64	
17	883	886	850	786		136	
18	856	860	849			7	
19	654	651	648			10	
20	557	569	565			16	
21	508	509	508	463		5	
22	327	327	323			19	
23	278	408	329			16	
24	91	177	144			3	

[a] Experimental data obtained in Ar matrix.[5] [b] Experimental O−H stretch obtained in He cluster.[6]

compared with 38 and 70 cm^{-1} for Ar matrix data. Such excellent agreement with the experiment in He droplets suggests that the errors of the calculations (which are partly due to the CC-VSCF method, but mostly are probably due to the inaccuracy of the potential) are smaller than the argon matrix effects.

The calculated vibrational spectra of the three glycine conformers are shown in Figure 2. Here we will mainly discuss the high-frequency parts of the calculated spectra, which correspond to the highest stretching vibrations. These vibrations are not described properly by the harmonic approximation, and the single-mode anharmonicities and coupling effects between the modes, accounted for by CC-VSCF, are very important. It can be seen from Figure 2 that while the highest frequency parts of the spectra are similar for conformers 1 and 3, the spectrum for conformer 2 is quite different, mostly due to the strong intramolecular hydrogen bond present in this conformer. The O−H bond which participates in the hydrogen bonding is elongated by 0.012 Å, and its corresponding vibrational frequency is red-shifted by 330−340 cm^{-1}, which is in very good agreement with experiment. The experimental value for the red shift is 360 cm^{-1} in Ar matrix and 304−310 cm^{-1} in He. Therefore, it can be concluded that the calculated red shift due to the intramolecular hydrogen bond is somewhat (25−30 cm^{-1}) overestimated compared with He cluster experimental data, but is still reproduced very well by the CC-VSCF method. Note that in Ar matrix the red shift for this frequency is much

TABLE 3: Vibrational Frequencies and IR Intensities for Glycine Conformer 3

mode	vibrational frequencies, cm^{-1} harmonic	VSCF	CC-VSCF	expt[a]	expt[b]	intensity, km/mol	description
1	3826	3581	3612	3560	3579	71	OH stretch
2	3681	3427	3393	3410		4	NH stretch asym
3	3579	3406	3360			2	NH stretch sym
4	3231	2992	2955			7	CH stretch asym
5	3167	2984	2931	2958		14	CH stretch sym
6	1833	1802	1800	1767		246	C═O stretch
7	1705	1764	1754	1630		34	HNH bend
8	1491	1598	1595	1429		3	HCH bend
9	1411	1419	1413			0	
10	1394	1368	1362	1339		45	
11	1373	1350	1346			40	
12	1210	1213	1207			0	
13	1200	1179	1163	1147		215	
14	1173	1147	1144	1101		20	
15	959	1035	1032			1	
16	925	958	938	883		188	
17	830	824	817	777		54	
18	703	780	734			124	
19	596	657	638			25	
20	521	598	593			55	
21	502	499	499	463		14	
22	309	436	241			18	
23	272	282	280			3	
24	9	65	56			0	

[a] Experimental data obtained in Ar matrix.[5] [b] Experimental O−H stretch obtained in He cluster.[6]

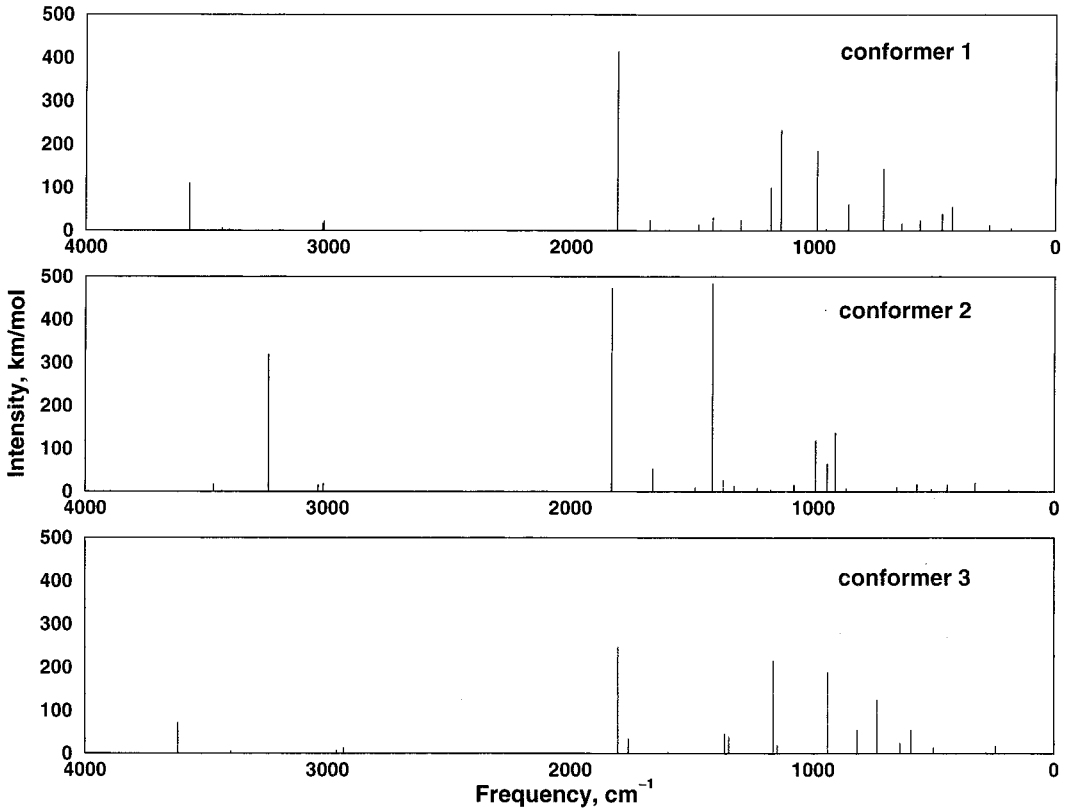

Figure 2. CC-VSCF vibrational spectra of glycine conformers calculated from MP2/DZP potential energy surfaces.

higher than in He, probably due to larger interactions of Ar atoms with the hydrogen-bonded O−H. It can be also seen from the Tables 1−3 and Figure 2 that the intensity of the red-shifted hydrogen-bonded O−H frequency in conformer 2 is enhanced by a factor of 3−4 compared with conformers 1 and 3. While OH stretch is the highest frequency vibration in conformers 1 and 3, its red shift in conformer 2 leads to this frequency falling below those of the NH stretches. The positions of the NH stretches (which have very low intensities compared with the OH stretch) change to a much lesser extent from one conformer to another. The changes of the asymmetric NH stretch are more pronounced, with its frequency being 35 and 46 cm^{-1} lower in conformers 1 and 3, respectively, than in the conformer 2. This may be attributed to a very weak (H-bonding) interaction of the N−H hydrogens with C═O and O−H oxygen atoms in conformers 1 and 3, which is not present in conformer 2. This intramolecular bond effect, where the NH_2 group serves as a proton donor and the O−H group as a proton acceptor, is much

weaker than the one in the conformer 2 where the roles of the O−H and NH_2 groups are reversed. Only one asymmetric NH frequency is observed experimentally and should probably be assigned to conformer 2, where its calculated intensity is somewhat higher. CH stretches also have very low intensities, and their positions are practically the same in conformers 1 and 2, with slightly lower values in conformer 3. The symmetric CH stretching frequency is in good correspondence with the one observed experimentally.

Although other vibrations of glycine are not so anharmonic as the highest stretches and are described by the harmonic approximation reasonably well, they are also somewhat improved by VSCF and CC-VSCF corrections. The corrections here are on the order of several tens of cm^{-1} rather than 200−250 cm^{-1} as for the OH, NH, and CH stretches, but they also bring the resulting frequencies into a closer agreement with experiment. The most intense and very characteristic C═O stretching vibration is worth mentioning. The CC-VSCF frequencies for conformers 1, 2, and 3 are 1805, 1824, and 1800, respectively. The relative order of the frequencies is in good accord with the corresponding order of experimental frequencies measured in Ar matrix (1779, 1790, and 1767),[5] but the absolute values of the computed frequencies are somewhat higher. The differences of about 30 cm^{-1} may be partially due to the inaccuracies of the potential energy surfaces at the ab initio level used here, and partially due to the Ar matrix effects that shift the stretching frequencies slightly to the red. The calculated frequencies for other (e.g., bending) vibrations are also higher than the ones measured in Ar by about the same amount. Our calculations also predict very high intensity for the vibration of conformer 2 that can be interpreted as a mixed stretching motion of C−C and C−O bonds and bending of COH fragment (the intensity of this vibration is much lower for conformers 1 and 3). Besides the OH stretch, which is red shifted and is more intense in conformer 2 than in the other two conformers, this very intense mixed vibration is another special feature of conformer 2 which perhaps can serve as its fingerprint.

In conclusion, the vibrational frequencies calculated using MP2/DZP level of ab initio and corrected for anharmonicities and mode−mode couplings by CC-VSCF are in very good agreement with experimental data and reproduce all the important differences between the glycine conformers correctly. We believe that the combined ab initio/VSCF method that allows calculation of anharmonic frequencies directly from an electronic structure program is far superior to the commonly used scaling techniques, where different scaling factors are applied to the very anharmonic stretching frequencies and to the rest of the frequencies described more reasonably at the harmonic level. Such empirical scaling "rules" are arbitrary and fail to predict the correct anharmonicities in systems where strong hydrogen bonding effects are present. Perhaps the most important conclusion from the results of this section is that the electronic structure method used, MP2 with the DZP basis set, gives very good agreement with spectroscopic experiments and thus seems to be producing a good anharmonic potential energy surface, at least over the region relevant to spectroscopy. This method can therefore be recommended as a standard tool for calculating potential energy surfaces and anharmonic vibrational spectra of small biological systems.

III.3. Comparison of ab Initio and OPLS Vibrational Spectra. Here, we use the experimental vibrational spectra to test another potential function, OPLS-AA (all atom),[19] one of the best empirical force fields available at the present time and widely used for simulations of biological systems. The vibrational state calculations are carried out by an algorithm similar to the one used for ab initio potential energy surfaces and anharmonic vibrational spectra. The structures of the three glycine conformers are optimized using the OPLS-AA empirical function, followed by the harmonic vibrational analysis and the calculations of the potential energy points needed to solve the VSCF equations and compute the anharmonic vibrational frequencies at the CC-VSCF level.

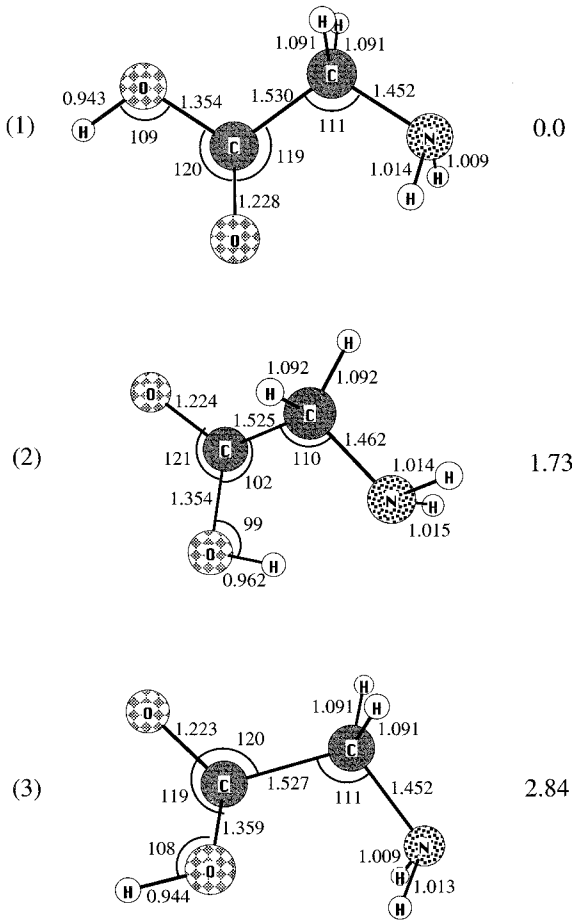

Figure 3. Equilibrium structures (Å, deg) and relative energies (kcal/mol) of the lowest energy conformers of glycine, obtained with OPLS-AA force field.

Equilibrium structures of the three glycine conformers, obtained using the OPLS-AA force field, are shown in Figure 3. It can be seen from the figure that bond lengths and bond angles are reproduced reasonably well by the OPLS-AA potential (compared to the MP2/DZP values, Figure 1). However, torsional angles predicted by OPLS-AA are very different and lead to the equilibrium structures, which are much more distorted from planarity than those predicted by ab initio calculations. This has a very important impact on vibrational spectra and is discussed further in the following paragraphs. It should be also noted that the OPLS-AA potential overestimates relative energies of conformers 2 and 3 with respect to the lowest conformer 1.

OPLS-AA vibrational frequencies for all three conformers are listed in Table 4 and compared with the ab initio (MP2/DZP) results and with experiment. As can be seen from the table, vibrational frequencies obtained with OPLS potential are very similar (practically indistinguishable) for all three conformers. This is in disagreement with the ab initio and experimental results, which show the existence of important differences between the vibrational spectra of the conformers. The reason

TABLE 4: Vibrational Frequencies (cm^{-1}) for Glycine Conformers: Comparison of ab Initio and OPLS[a]

	conformer 1			conformer 2			conformer 3			
mode	ab initio	OPLS	expt	ab initio	OPLS	expt	ab initio	OPLS	expt	description
1	3598	3701	3560	3270	3662	3200	3612	3683	3560	OH stretch
2	3382	3279	3410	3428	3277	3410	3393	3279	3410	NH stretch asym
3	3343	3259		3360	3256		3360	3257		NH stretch sym
4	2986	2953		2989	2947		2955	2952		CH stretch asym
5	2959	2899	2958	2958	2887	2958	2931	2895	2958	CH stretch sym
6	1805	1628	1779	1824	1638	1790	1800	1636	1767	C═O stretch
7	1669	1592	1630	1653	1607	1622	1754	1586	1630	HNH bend
8	1473	1494	1429	1483	1448	1429	1595	1445	1429	HCH bend
9	1410	1381	1373	1399	1401	1390	1413	1393		
10	1377	1246		1363	1283		1362	1269	1339	
11	1290	1093		1317	1111		1346	1080		
12	1185	1070		1219	1079	1210	1207	1045		
13	1167	1044	1136	1166	1030	1130	1163	1040	1147	
14	1122	991	1101	1073	1007		1144	994	1101	
15	970	968	907	976	892	911	1032	947		
16	943	838	883	926	872	880	938	855	883	
17	847	753	801	850	781	786	817	754	777	
18	633	571	619	849	769		734	550		
19	613	455		648	556		638	427		
20	514	449	500	565	472		593	442		
21	463	390	463	508	355	463	499	387	463	
22	352	329		329	349		280	325		
23	270	318		323	268		241	321		
24	143	176		144	169		67	145		

[a] Vibrational frequencies are calculated using the CC-VSCF method.

for this failure is the inability of the OPLS-AA force field to describe the subtle (but very important) effects of the intramolecular hydrogen bonding present in this molecule. OPLS-AA, as well as other empirical force fields currently used for studies of biological systems (AMBER,[20] CHARMM,[21] etc.) are not parametrized to account for such interactions.

The failure of the OPLS-AA potential to describe intramolecular hydrogen bonding effects leads to the equilibrium geometries, which are significantly twisted around the C−C bond and distorted from C_s symmetry. This especially affects conformer 2, where ab initio calculations predict the strongest intramolecular hydrogen bonding, which leads to the substantial red shift of the O−H stretching frequency. This effect does not exist in the case of the OPLS-AA potential, and therefore this conformer has a vibrational spectrum very similar to the spectra of the other two conformers, with the O−H stretch being the highest frequency vibration. Other (more subtle) differences between the conformers (correctly predicted by ab initio VSCF calculation), are also not reproduced by OPLS-AA. For example, ab initio C═O stretching frequencies, though higher by about 35 cm^{-1} compared with Ar matrix values, change consistently from one conformer to another in agreement with experiment. OPLS-AA frequencies for C═O stretches do not show the correct trends for different conformers. They are much closer to each other in all three conformers, and in addition to this, they are greatly underestimated (by about 150 cm^{-1}). N−H and C−H stretching frequencies calculated using OPLS-AA potential are also significantly underestimated.

The differences between vibrational spectra predicted using the same (CC-VSCF) method but different (ab initio MP2/DZP and empirical OPLS-AA) potentials come from two sources: one is the difference in the equilibrium geometrical structures, which leads to substantial differences between vibrational spectra already at the harmonic level; the second is the different shapes of the potential energy surfaces further from equilibrium, which lead to very different anharmonic corrections. We have discussed already the failure of the OPLS potential to predict the correct equilibrium structure of conformer 2 due to the incorrect description of hydrogen-bonding interactions. This failure occurs already at the harmonic region. However, there are also very significant differences between the ab initio and OPLS potentials in the regions where anharmonicities are much larger. The anharmonic effects are not described by this empirical potential properly, even for the conformers where the harmonic description is reasonable. Single-mode ("diagonal") anharmonicities are quite substantial for the highest stretching modes in the case of ab initio potential, with the highest one corresponding to O−H stretch (almost 200 cm^{-1}) and the ones for N−H and C−H stretches being on the order of 60−80 cm^{-1}. These anharmonic corrections are nonexistent in the case of OPLS potential, since such empirical potentials are defined as harmonic functions. Anharmonic corrections due to couplings between normal modes (calculated in this study within the pairwise approximation) are more significant than the one-dimensional anharmonic corrections, both in the cases of ab initio and empirical potentials. Such corrections play a crucial role in improving the calculated vibrational frequencies and bringing them to a closer agreement with experiment. The differences between the pair coupling corrections obtained with ab initio and OPLS potentials are also very large. The ab initio pair coupling corrections for the highest stretches are very substantial (they are on the order of 100 cm^{-1} for symmetric stretches and up to 250−300 cm^{-1} for asymmetric stretches). The pair coupling corrections calculated with OPLS potential for the same vibrations are much smaller (30−70 cm^{-1}). This suggests that the empirical potentials such as OPLS not only fail to describe the equilibrium structures and harmonic vibrational spectra in some cases, but are even more unphysical in the regions far from equilibrium, where anharmonic effects are important. This conclusion may have very important implications for modeling of biomolecular systems. Very often molecular dynamics and other simulations are carried out for processes governed by the potential in regions far from the equilibrium geometries. It seems that the empirical force fields are even more suspect for such situations than for those corresponding to near-equilibrium geometries.

III.4. Coupling between Normal Modes. As we already mentioned in the previous section, pair coupling anharmonic effects are very important and their effect on vibrational frequencies is more significant than the effect of one-dimensional anharmonicities. In this section we present a more detailed analysis of anharmonic couplings between different normal modes and their effect on vibrational frequencies of glycine conformers. One objective is to characterize the relative "strength" of the coupling between different normal modes and find out which normal modes in this molecular system are most strongly coupled. Such analysis can be useful for several purposes. First, it can give some insight into the nature of anharmonic couplings, which can perhaps be generalized to other biological molecules as well, for example, larger amino acids. Second, it can be useful from a practical point of view. Since the computation of pair coupling potential is the most expensive part of ab initio VSCF procedure and scales as $N(N-1)/2$ (where N is the number of normal modes), it is very important to know for which pairs of modes coupling potential is necessary to compute, and for which it can possibly be excluded from calculations without affecting the resulting vibrational frequencies.

We considered several criteria that can be used to characterize relative "coupling strengths". One is the root-mean-square (rms) value of the pair coupling potential $\bar{V}_{ij}^{\text{coup}}(Q_i,Q_j)$ from eq 3 calculated over N_{grid}^2 points for each pair of normal modes i and j. In the second criterion, this rms potential value is divided by the difference of vibrational frequencies of the corresponding mode excitations: $\bar{V}_{ij}^{\text{coup}}(Q_i,Q_j)/(\omega_i - \omega_j)$. The second criterion is dimensionless and represents the fact that a given strength of coupling has a greater effect for excitations that are nearly degenerate. The third criterion considered here is the effect of removing pair coupling terms for certain pairs of modes from the results of CC-VSCF calculations. The last criterion is the most rigorous, since excluding some pair-coupling terms from VSCF and CC-VSCF expressions affects total energies of both ground and excited vibrational states and therefore shows how vibrational frequencies change when certain couplings are removed from the calculation. However, applying this criterion to all pairs of modes is very tedious, and it is used in this study to estimate the importance of couplings between only a few selected pairs of modes.

The results obtained using the second ($\bar{V}_{ij}^{\text{coup}}/(\omega_i - \omega_j)$) criterion for ab initio coupling potentials of conformers 1 and 2 are presented in Figures 4 and 5. In these figures matrices are shown, the rows and columns of which carry as labels the mode numbers from 1 to 24 (from the highest to the lowest frequency vibration). Only couplings for which $\bar{V}_{ij}^{\text{coup}}/(\omega_i - \omega_j)$ is greater than 50 are shown and denoted by S (strong). The threshold value of 50 is arbitrary to some extent, but applying the more rigorous (third) criterion to several selected pairs of modes showed that removing the pair coupling terms that correspond to $\bar{V}_{ij}^{\text{coup}}/(\omega_i - \omega_j)$ values less than 50 from CC-VSCF calculation leads to very small (not larger than a few cm^{-1}) changes of the resulting vibrational frequencies, and therefore such pair couplings can be considered weak. It can be seen from Figures 4 and 5 that matrices of strong couplings are rather sparse. Most of the strong couplings are concentrated near the diagonal of the matrix; that is, the normal modes with closer frequencies are more strongly coupled. Also, it can be seen from the matrices that in both conformers the high-frequency stretching vibrations (O−H, N−H, and C−H stretches: mode numbers 1−5) are strongly coupled with some bending vibrations and with the lowest frequency torsional

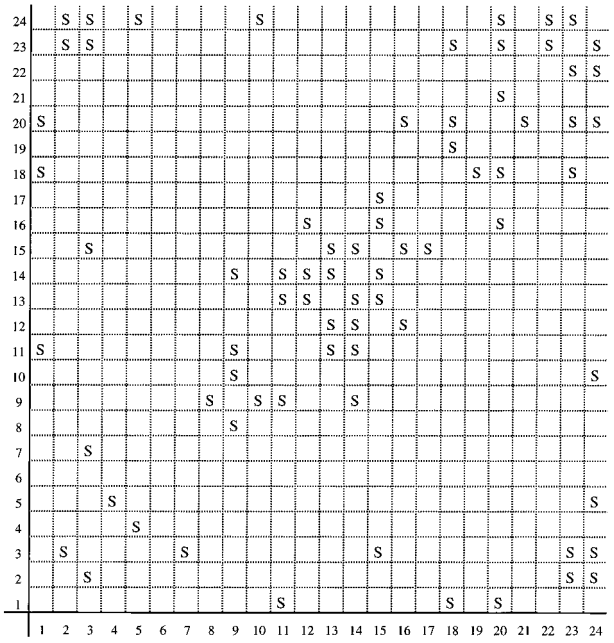

Figure 4. Strength of the ab initio pair coupling potentials for glycine conformer 1. S (strong) correspond to values of $\bar{V}_{ij}^{\text{coup}}/(\omega_i - \omega_j) > 50$. The mode numbers are arranged according to decreasing vibrational frequency.

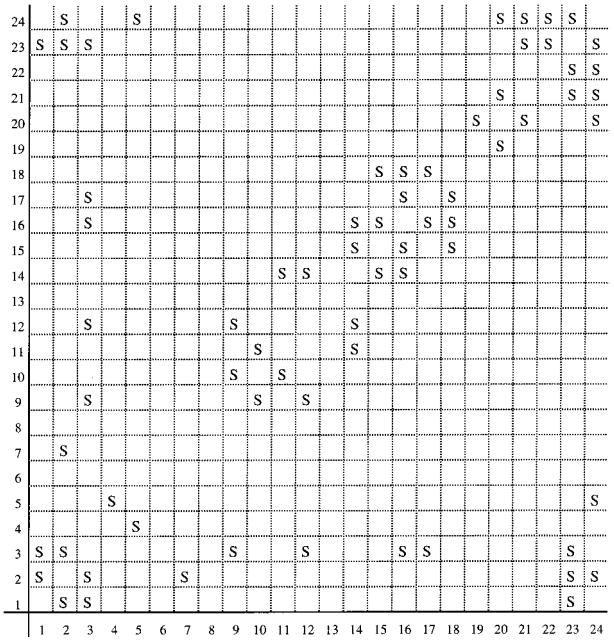

Figure 5. Strength of the ab initio pair coupling potentials for glycine conformer 2. S (strong) correspond to values of $\bar{V}_{ij}^{\text{coup}}/(\omega_i - \omega_j) > 50$. The mode numbers are arranged according to decreasing vibrational frequency.

modes. Strong couplings are also present between low-frequency modes (numbers 20−24) that correspond to torsional motions.

Matrices of "strong couplings" for conformers 1 and 2 calculated from OPLS-AA potential and based on the same threshold criterion are shown in Figures 6 and 7. The pictures here are very different from the corresponding matrices for the ab initio case. Much larger number of pairs of normal modes appear to be strongly coupled in this case, although removing the corresponding pair coupling terms from CC-VSCF calculation does not change the resulting frequencies significantly. This is another interesting feature that is different for ab initio and empirical potentials and may have more important implications

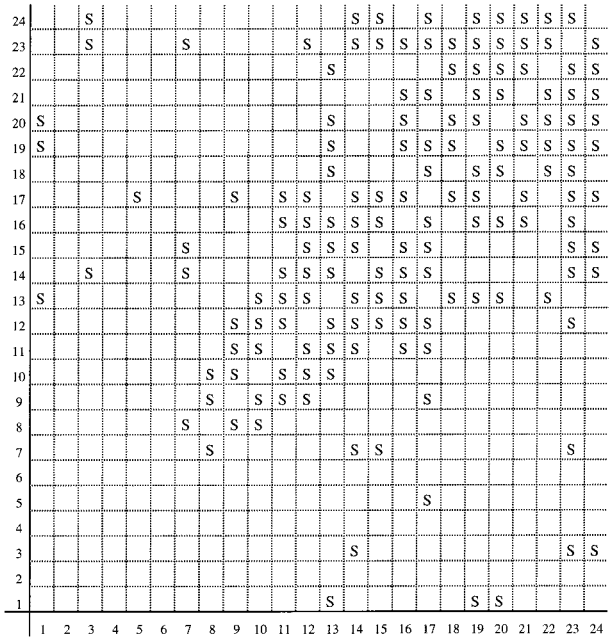

Figure 6. Strength of the OPLA-AA pair coupling potentials for glycine conformer 1. S (strong) correspond to values of $\bar{V}_{ij}^{\mathrm{coup}}/(\omega_i - \omega_j) > 50$. The mode numbers are arranged according to decreasing vibrational frequency.

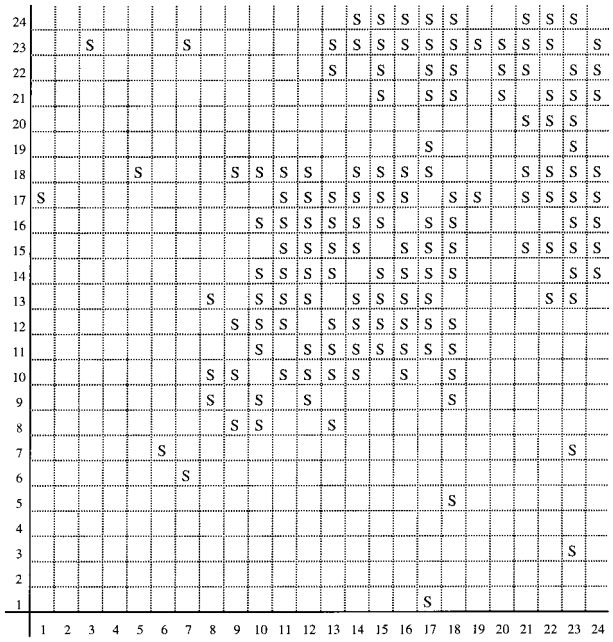

Figure 7. Strength of the OPLA-AA pair coupling potentials for glycine conformer 2. S (strong) correspond to values of $\bar{V}_{ij}^{\mathrm{coup}}/(\omega_i - \omega_j) > 50$. The mode numbers are arranged according to decreasing vibrational frequency.

to dynamics of intramolecular energy transfer. Energy flow between different normal modes is entirely due to anharmonic couplings. Thus energy flow in biological molecules may be incorrectly described by presently available empirical force fields.

Here we use the third criterion (described above) to analyze coupling strengths between different high-frequency modes. It is found that among the strongest are couplings between the two (symmetric and asymmetric) N−H stretches, between the two C−H stretches, and the coupling between the symmetric N−H stretch and the NH_2 bend. On the other hand, the couplings between the high-frequency modes that correspond to different

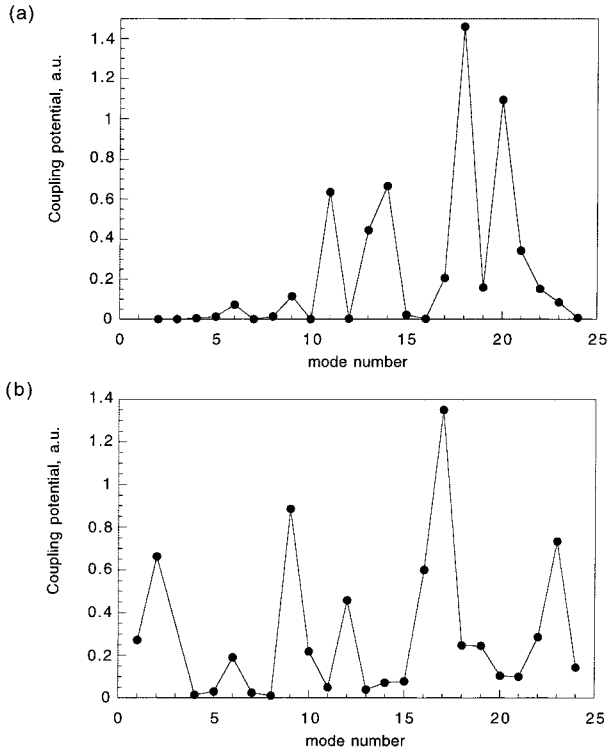

Figure 8. Root-mean-square (rms) values of pair coupling potentials $\bar{V}_{ij}^{\mathrm{coup}}$ of OH strecthing vibration with all other modes: (a) conformer 1; (b) conformer 2.

chemical groups well separated in space are weak and can be ignored without affecting the resulting frequencies. For example, in conformer 1, removing the pair coupling potential terms, which include the OH stretch and one of the NH stretches, from the CC-VSCF calculation, does not change the resulting frequencies at all. Excluding the contributions of pair coupling potentials between the OH stretch and one of the CH stretches leads to negligible changes (not larger than 1 cm^{-1}) of the CH stretching frequencies. Ignoring couplings between NH and CH stretches produces slightly larger, but still negligible errors of up to 2−3 cm^{-1}. The situation is very different in conformer 2, when the hydrogen-bonded OH stretch is decoupled from the NH stretching modes. In this case, the error is very substantial. Such decoupling leads to underestimation of the NH stretching frequencies by 20 cm^{-1} and overestimation of the OH frequency by almost 100 cm^{-1}. This shows the importance of coupling interactions between the stretching modes in the cases where the corresponding parts of the potential energy surface are affected by hydrogen bonding. In such cases, the pair coupling potential terms play a crucial role and cannot be neglected. Another illustration of the differences in pair coupling potentials between conformers 1 and 2 is presented in Figure 8. Here, the plotted rms average pair coupling potential values $\bar{V}_{ij}^{\mathrm{coup}}$ are between the O−H stretching vibration and other vibrational modes. It is also seen from this figure that O−H stretch is practically not coupled with N−H stretches in conformer 1, while in conformer 2 such couplings are substantial.

We believe that many of the features of the mode−mode couplings found for glycine conformers should be also present in other similar molecular systems, for example, larger amino acids such as alanine and valine. The information obtained for glycine molecule can help to construct approximate pair coupling potentials for such larger molecules (where full ab initio calculation becomes prohibitively expensive) and to predict their anharmonic vibrational spectra.

IV. Conclusions

In this paper, anharmonic vibrational spectra are calculated for the three lowest conformers of the simplest amino acid glycine using a combination of the correlation corrected vibrational self-consistent field (CC-VSCF) method with direct calculation of ab initio potentials at the MP2/DZP level. The results of the calculations are in a very good agreement with experimental IR spectra measured for glycine conformers trapped in an Ar matrix, the average deviations being of the order of 25−30 cm^{-1}. The calculated O−H stretching frequencies are in closer agreement with experimental frequencies obtained in superfluid He clusters, where the effects of matrix environment are minimal.

The effects of hydrogen bonding on vibrational frequencies are analyzed. Hydrogen bonding interactions are very important for the correct description of the potential energy surfaces and are the main source of the differences in the geometry and vibrational spectra of the glycine conformers. Effects of intramolecular hydrogen bonding on vibrational spectra are found to be very important and can serve as important fingerprints of different conformations of biological molecules. Influence of intramolecular hydrogen bonding on structural and vibrational properties of aromatic amino acids (such as phenylalanine) and other biological molecules (with amino and OH groups present) is shown to be even stronger than in the case of aliphatic amino acids.[22,23] Such intramolecular hydrogen bonding present in the side chains of aromatic biological molecules inverses the stability of the conformers of the type 1 and 2, making hydrogen-bonded structure 2 more stable.

Vibrational spectroscopy is a very sensitive property and can serve as a test of the quality of the potential energy surfaces. Indeed, as the present paper shows, vibrational spectroscopy can sensitively test the anharmonic part of potential energy surfaces, which is of particular interest. Comparison of the calculated results with experimental IR spectra shows that ab initio potential energy surfaces used in this study (at the level of second-order Møller−Plesset perturbation theory with the double-ζ basis set) describe the subtle effects of hydrogen bonding correctly and predict the important differences of vibrational spectra of glycine conformers in very good accordance with experiment. This level of ab initio theory can be recommended for studies of potential energy surfaces and vibrational spectra of other small biological molecules. As emphasized, the spectroscopic support of the MP2 potential pertains also to the anharmonic part of the interactions.

On the other hand, the results obtained using the empirical OPLS-AA potential are much less satisfactory. This potential fails to predict many important features and differences of the experimental vibrational spectra of glycine conformers, mostly due to its inability to describe the effects of the intramolecular hydrogen bonding. In addition, the regions of the potential energy surfaces which are far from equilibrium and are more anharmonic are also incorrectly described by this empirical force field. These weaknesses of the empirical potentials make them unreliable for predicting not only vibrational spectra of small biological molecules, but also other properties such as vibrational energy flow between different normal modes. The results of this paper strongly suggest that in the future it may be desirable to base modeling of small biological molecules on ab initio potentials, rather than on empirical ones commonly used in the present state of the art.

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