$\theta_e(\mathrm{HC = N}) = 118.8°$, and cis $\theta_e(\mathrm{HC = N}) = 124.6°$.[24] Thus it seems clear that the singlet electronic state is the species responsible for the widely recognized extreme reactivity[1-4] of methylnitrene. In this sense it appears that singlet alkylnitrenes are even more susceptible to 1,2 hydrogen shifts that the comparable alkylcarbenes, which have small but finite barriers to isomerization.[13]

More complete levels of theory were also applied to ^1E CH_3N and ground state $CH_2{=}NH$, and the results are summarized in Table II. The singlet predictions, at the unlinked cluster corrected DZ + P CI level of theory, are included with the triplet results in Figure 2, an electronic state energy level diagram. Figure 2 illustrates particularly clearly the crossing of the triplet and singlet potential surfaces during the CH_3N isomerization. Should the $^3A''$ and $^1A'$ states be connected sufficiently strongly by spin–orbit coupling or some other interaction, a crossing from the triplet to singlet potential energy surface might occur.

Among recent experimental studies[25-30] designed to test whether alkylnitrenes exist as discrete intermediates, one aspect of the widely cited[2,3] work of Moriarty and Reardon[25] stands in contradiction to the present theoretical predictions. Examining the products of photolysis of ten alkyl azides including the *n*-butyl compound, Moriarty and Reardon concluded that migration of the α substituent occurs synchronously with the departure of molecular nitrogen. The seemingly inexplicable result of their experiments is that the triplet photosensitized process, designed to generate a triplet nitrene intermediate, yielded the same product distribution as the direct photolytic decomposition. In spite of the above experimental data, it seems extremely unlikely to us that the room-temperature triplet 1,2 hydrogen shift of *n*-butyl nitrene could occur with the rate constant suggested,[25] namely, $10^6\ s^{-1}$.

This apparent conflict with the experiments of Moriarty and Reardon[25] might be explained if the triplet decomposition of the alkyl azide is concerted or if the "triplet" sensitization actually involves energy transfer from a singlet, which is not an impossible occurrence with polycyclic aromatic sensitizers. Moriarty and Reardon (page 1384, ref 25) note that the triplet photosensitizer chrysene may actually yield the singlet state of the azide.

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Ab Initio Self-Consistent Field Calculations on Some Small Amino Acids

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Abstract: Ab initio self-consistent field calculations have been performed on five small amino acids: glycine, alanine, serine, cysteine, and threonine. SCF energies are reported for the nonionic and zwitterionic forms of the molecules using a split-valence 6-31G Gaussian basis set. The ionization potential, proton affinity, and dipole moment were computed for each amino acid. The gaseous zwitterion of each amino acid was calculated to be 34–43 kcal/mol less stable than the neutral form. The difference in energy between the neutral and zwitterionic forms of the amino acids was used to determine the energy difference between the gaseous zwitterion and its solid and solvated states. The calculated properties of the neutral amino acids varied slightly among the five studied: the average ionization potential was 8.3 ± 0.6 eV and the average proton affinity was 222 ± 4 kcal/mol. The individual differences are consistent with the inductive effects of the amino acid side chains. Comparison between other computational and experimental results is also given.

Introduction

Ab initio self-consistent field (SCF) calculations have frequently been performed on atoms and small molecules, but only in recent years have these calculations been extended to larger polyatomic molecules. This is due in large part to advances made in the speed and capacity of computers and increased efficiency in software. A class of molecules now feasible to study at the ab initio theoretical level are those of biological interest; amino acids, $NH_2CHRCOOH$, for example, are ideally suited for this purpose.

Glycine (R = H), the smallest amino acid, has been the subject of several ab initio calculations. The conformation, relative energetics, and SCF energies of glycine and its zwitterion have been computed using a 4-31G Gaussian basis set.[1,2] Ryan and Whitten have studied the nature of the bonding in the glycine zwitterion and in the simplest dipeptide, glycylglycine, using both SCF and limited CI techniques.[3] Semiempirical molecular orbital theory has also been used to study glycine: Oegerle and Sabin have performed CNDO calculations to determine the conformation and molecular properties of this amino acid,[4] while Chung et al. employed the INDO method to study the protonation of glycine.[5] Examples of other theoretical calculations on glycine include extended Hückel molecular orbital theory[6] and the ab initio

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Table I. Calculated SCF Energies and Dipole Moments of the Five Neutral Amino Acids and Their Zwitterions in the Gas Phase

	neutral		zwitterion		
amino acid	energy, au	dipole moment, D	energy, au	dipole moment, D	ΔE,[a] kcal/mol
glycine	−282.688 47	1.77	−282.619 95	13.85	42.99
alanine	−321.710 41	1.83	−321.644 56	13.45	41.32
serine	−396.517 53	2.22	−396.462 75	12.91	34.37
cysteine	−718.731 37	1.96	−718.677 59	12.47	33.74
threonine	−435.541 19	2.04	−435.485 47	12.78	34.96

[a] The gas-phase difference between the neutral and zwitterionic amino acids, $E(^+A^-) - E(A)$, in kcal/mol.

molecular fragment approach.[7] Glycine was also used as a test molecule in calculations employing charge-conserving integral approximations.[8] More recently, Palla et al. compared the results of several theoretical approaches used in the study of internal rotation in glycine.[9]

Calculations on other amino acids are more limited. Ab initio SCF energies have been reported for 21 neutral amino acids[10] and for the glycine and serine zwitterions[11] using a contracted Gaussian basis set with a number of time-saving, approximate integral routines. The results of these calculations were subsequently used to study the interaction of water with these amino acids.[10,11] The nonempirical PRDDO method was employed in the calculation of the electronic structure and bonding of several amino acids.[12]

Herein are presented results of accurate, completely ab initio SCF calculations on five amino acids: glycine (R = H), alanine (R = CH_3), serine (R = CH_2OH), cysteine (R = CH_2SH), and threonine (R = CH_3CHOH). SCF energies and dipole moments are given for both the nonionic and zwitterionic forms of the molecules; ionization potentials and proton affinities are computed for the neutral amino acids. Estimates of the energy required for the transition of the solid amino acid to the gaseous zwitterion and the energy released when the gaseous zwitterion is solvated are also given.

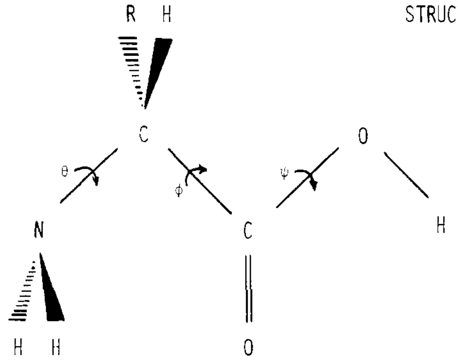
There are currently few experimental results in the literature for amino acids larger than glycine. Glycine has, however, been widely studied. Thus, to assess the accuracy of the calculated properties of the larger amino acids studied here, glycine was investigated in order to compare with the available experimental results.

Method of Calculation

All calculations were performed on a Control Data Cyber 70, Model 74, computer. The calculations employed the HONDO (Version 5.0) program written by Dupuis et al.[13] using the restricted SCF techniques developed by Roothaan.[14] A split-valence 6-31G Gaussian basis set was used for all atoms with the exception of sulfur and hydrogen, where the 4-31G and 31G basis sets were used, respectively.[15] To determine the quality of the 6-31G basis set, test calculations were performed on N_2, CO, and H_2CO; these calculations gave results within 0.13% of the Hartree–Fock energies of these molecules.[16] It is believed that the energies reported for the five amino acids in the present work are of comparable quality.

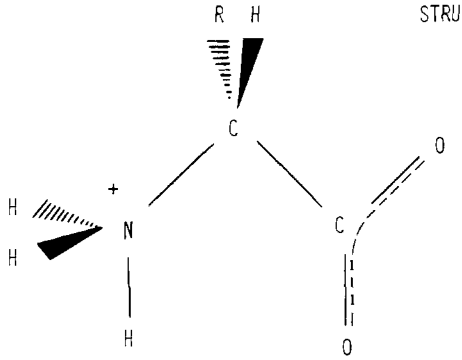
Bond lengths and angles were taken from the standard values given by Pople and Gordon,[17] where available. For sulfur, the following bond lengths were used: S–H, 1.34 Å, and S–C, 1.82 Å;[18] the S2 angle was taken to be 109.47°. Use of the standard geometric parameters resulted in the heavy atoms of glycine lying in a plane. By varying the dihedral angles, Vishveshwara and Pople, using a 4-31G basis set, calculated the most stable orientations of the neutral glycine molecule and its zwitterion,[1,2] as depicted in structures I and II. Calculations carried out using the 4-21G[19] as well as the present 6-31G basis sets concurred with these results. These conformations, therefore, were adopted for the other amino acids studied. Use of the standard bond lengths and angles resulted in the heavy atoms of the R-group side chains also being planar. The side chains were chosen to be oriented in a plane parallel to that of the glycine fragment in an effort to minimize steric interactions. This approach was adopted as it was felt that a complete study of the rotation barriers of each of the amino acids would be prohibitively expensive. The calculations consumed from 4200 CPU seconds per SCF energy for glycine to over 30 000 CPU seconds per SCF energy for threonine.

STRUCTURE I



θ = φ = ψ = 0°

STRUCTURE II



Convergence of the SCF iterative cycles has been a considerable problem in previous calculations on polyatomic molecules. Some recent refinements made in computer programs are directly related to this problem.[1] By properly choosing the initial guess input vectors, however, one can effectively avoid most difficulties in convergence. This has been the case in each of the amino acids studied here. Using alanine as an example, appropriate vectors from calculations on glycine and methane were combined and used as the initial guess coefficients. The glycine vectors were, in turn, generated from calculations which used methylamine and formic acid vectors as starting coefficients. Once obtained, these vectors were used for the calculation of the zwitterion as well as for the singly positive and protonated species. In this way, the number of iterations required to achieve convergence was typically reduced by 30–50%.

Results

The SCF energies for the neutral and zwitterionic forms of the amino acids are presented in Table I along with the computed dipole moments. For each of the five amino acids, the gaseous zwitterion was calculated to be 34–43 kcal/mol less stable than the neutral molecule. A comparison of the energies of glycine

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Table **II**. Comparison of Previous Calculations on Glycine and the Glycine Zwitterion with Present Results

glycine calcn	basis set or method used	energy, au neutral	zwitterion
DL[a]	PRDDO	−281.727	
CCS/CCPC[b,c]	contracted Gaussian	−281.779	−281.684
WE[d]	charge conserving integral approximations		−282.119 23
SS[e]	4-21G	−282.158 05	
RW (SCF)[f]	3s/1p		−282.120 5
RW (CI)[f]	3s/1p		−282.168 9
VP/TNVP[g,h]	4-31G	−282.400 77	−282.354 24
present work	6-31G	−282.688 47	−282.619 95
Hartree-Fock (estd)[i]		−283.05	−282.98

[a] Reference 12. [b] Reference 10. [c] Reference 11. [d] Reference 8. [e] Reference 19. [f] Reference 3. [g] Reference 1. [h] Reference 2. [i] This estimate is based on the results of calculations on molecules whose Hartree-Fock energies are known; see text.

Table **III**. Calculated SCF Rotation Barriers of the Glycine Molecule, Relative to the Most Stable Orientation. Comparison between the Results of the 4-31G and 6-31G Basis Set Calculations

conformation[a] angle, deg θ	ϕ	ψ	4-31G,[b] kcal/mol	6-31G,[c] kcal/mol
0	0	0	0.0	0.0
180	0	0	8.1	8.2
0	180	0	2.6	2.7
180	180	0	7.5	7.9
180	180	180	2.2	2.5

[a] The geometric parameters are defined in structure I. [b] Reference 1. [c] Present work.

Table **IV**. Calculated SCF Ionization Potentials for the Amino Acids

amino acid	neutral direct,[a] eV	Koopmans'[b,c] theorem, eV	zwitterion Koopmans'[b] theorem, eV
glycine	8.61	10.15 (10.0)	8.77
alanine	8.46	10.09 (9.8)	8.77
serine	8.76	10.33	9.51
cysteine	8.00	9.47	8.88
threonine	*d*	10.23	8.69

[a] Calculated ionization potential from $E(\mathrm{A}) - E(\mathrm{A}^+)$. [b] Ionization potential computed using Koopmans' theorem and the "8% rule". [c] Experimental values in parentheses from ref 25. [d] Omitted because of excessive computation time required.

and its zwitterion calculated using a 6-31G basis set with the results of previous calculations is summarized in Table II. The present SCF energy for glycine was 8–25 eV lower than previous theoretical calculations and was estimated to lie about 10 eV above the Hartree–Fock limit (see Table II).

A number of glycine conformations were studied using the 6-31G basis set to determine the most stable orientation of the neutral molecule. A summary of the calculated values of the rotation barriers is presented in Table III. The dihedral angles θ, ϕ, and ψ are defined in structure I; the most stable orientation is the one in which $\theta = \phi = \psi = 0°$. The results of these calculations were within 0.5 kcal/mol to those of Vishveshwara Pople, who used the smaller 4-31G basis set.[1]

The first vertical ionization potential for each amino acid is presented in Table IV. The ionization potential was determined in two ways: first as the difference between SCF calculations on the neutral and the singly positive amino acid, and second by using Koopmans' theorem[20] and the empirically determined "8% rule".[21] The two methods predicted the same trend in ionization potentials, but differed in each case by about 1.55 eV, with the directly calculated ionization potential being the smaller of the two. The ionization potentials of the zwitterions were computed using only the Koopmans' theorem/"8% rule" approach. These ionization potentials, included in Table IV, are seen to be lower than the values for the corresponding neutral molecules by an average of 1.1 eV.

Table **V**. Calculated SCF Proton Affinities for the Protonation of the Nitrogen Atom of the Neutral Amino Acids

amino acid	proton affinity,[a] kcal/mol	internuclear distance,[b] Å
glycine	222.30 (208.2)	1.012
alanine	225.78 (212.2)	0.987
serine	219.99	1.017
cysteine	219.76	1.011
threonine	221.04	1.014

[a] Experimental values in parentheses from ref 24. [b] The distance between the proton (tetrahedral approach) and the nitrogen atom of the neutral amino acid.

Table **VI**. Calculated SCF Energy Differences between the Gaseous Zwitterions and Their Solid and Solvated States[a]

amino acid zwitterion	ΔE, kcal/mol $[^+\mathrm{A}^-{}_{(s)} \rightarrow {}^+\mathrm{A}^-{}_{(g)}]$	$[^+\mathrm{A}^-{}_{(g)} \rightarrow {}^+\mathrm{A}^-{}_{(aq)}]$
glycine	66.0	−62.2
alanine	66.3	−64.5
serine	54.5	−49.2
cysteine	56.7	−51.2
threonine	58.0	*b*

[a] Determined by combining the calculated neutral and zwitterion energies in Table I with the experimental data of ref 22. [b] $\Delta H_{(\mathrm{soln})}$ for threonine was not given.

Reported in Table V is the minimum SCF energy and the equilibrium internuclear distance for the tetrahedral approach of a proton to the nitrogen atom of each neutral amino acid. These interaction energies were calculated at 3–4 internuclear distances. The proton affinities were then determined from the minima in curves fit smoothly through these computed points. The proton affinities were remarkably constant for the five amino acids studied, with an average value of 222 ± 4 kcal/mol. The energy barrier to rotation of the protonated amine group about the C–N axis of glycine was calculated to be less than 0.2 kcal/mol. This barrier was not calculated for the other four amino acids.

The energy associated with the transition of the solid amino acid to the gaseous zwitterion, $[^+\mathrm{A}^-{}_{(s)} \rightarrow {}^+\mathrm{A}^-{}_{(g)}]$, and the heat evolved when this gaseous species is solvated, $[^+\mathrm{A}^-{}_{(g)} \rightarrow {}^+\mathrm{A}^-{}_{(aq)}]$, have been estimated by combining the present calculated energies of the neutral and zwitterionic amino acids with the experimental data of Gaffney et al.[22] These estimated energies are given in Table VI. The values for glycine and alanine are noted to be much larger (about 20%) than those for the other amino acids.

Discussion

The use of the 6-31G basis set has resulted in a significant improvement in the SCF energies calculated for the amino acids compared to the other split-valence basis sets previously used, without increasing the total number of basis functions. The SCF energy reported for glycine using a 4-21G basis set, −282.15805 au,[19] is about 6.6 eV higher than the result computed with a 4-31G basis set, −282.40077 au.[1] The 6-31G basis set used in the present work lowered this energy by an additional 7.8 eV (see Table II). This energy improvement did not come at the cost of a substantial increase in computation time. Calculations on glycine comparing the 4-31G and 6-31G basis sets showed only a 6% increase in

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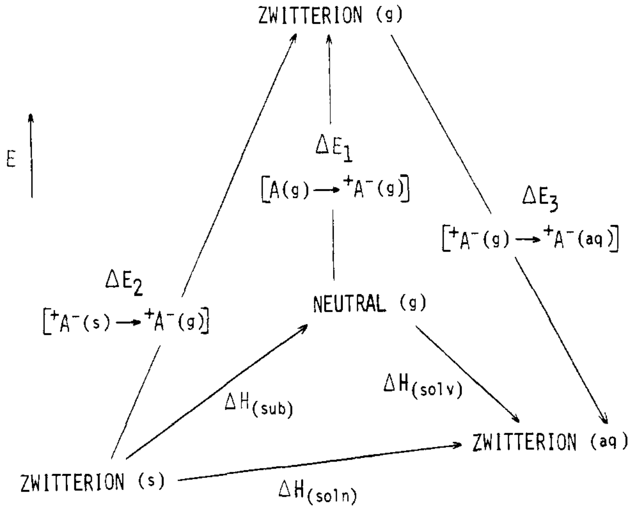

Figure 1. Energy level diagram for the transitions of the solid amino acids to the gaseous and solvated states. The experimental enthalpies, ΔH_{sub}, ΔH_{soln}, and ΔH_{solv}, were taken from ref 24. The difference in energy between the gaseous neutral and zwitterionic amino acids, ΔE_1, has been combined with the experimental enthalpies to estimate ΔE_2 and ΔE_3.

computation time. As indicated previously, the SCF energies obtained for glycine and the other amino acids in Table I using a 6-31G basis set are believed to be within 0.13% of the Hartree–Fock energies.

The difference in energy between glycine and the glycine zwitterion has been the subject of much interest.[2] In the crystalline state and in solution, glycine normally exists as a zwitterion in contrast to the neutral form preferred in the gas phase. The calculated energy differences between the gas-phase neutral and zwitterion species vary considerably among the various theoretical predictions. The semiempirical methods result in differences of 101,[4] 73,[23] and 67[5] kcal/mol, with the neutral species being more stable. Ab initio calculations report smaller energy differences between the two species of 57[10,11] and 29[2] kcal/mol, while the present work puts this value at 43 kcal/mol. Again, the neutral molecule is predicted to have the lower energy. The difference in energy between the gaseous neutral and zwitterionic amino acids has not been experimentally determined, but the calculated energy differences can be used together with the experimental heats of sublimation and heats of solution to provide estimates of the energies associated with the transition of the solid amino acid to the gaseous zwitterion, $[{}^{+}A^{-}_{(s)} \rightarrow {}^{+}A^{-}_{(g)}]$, and the solvation energy of the gaseous zwitterion, $[{}^{+}A^{-}_{(g)} \rightarrow {}^{+}A^{-}_{(aq)}]$. These quantities are depicted in Figure 1 and the estimates for each amino acid studied are reported in Table VI. The predicted energy difference between the gaseous glycine zwitterion and the solvated ion, −62.2 kcal/mol, is about 14 kcal/mol larger than that estimated by Gaffney et al.[22] using the calculated results of Tse et al.[2] No previous estimates are available for comparison for the other amino acids studied here.

The zwitterions of the amino acids with polar side chains (serine, cysteine, and threonine) were about 8 kcal/mol more stable than those with nonpolar R groups (glycine and alanine), relative to the neutral molecules (see Table I). The hydroxyl groups of serine and threonine and the sulfhydral group of cysteine apparently serve to distribute the charge of the zwitterion over a greater volume, thus stabilizing the entire molecule. This effect can also be observed to a lesser extent in the computed dipole moments; the dipole moments given in Table I of the glycine and alanine zwitterions are larger than those of the other three amino acids, presumably owing to the greater charge separation. This charge stabilization also has an effect on the solvation energies (see Table IV). The work of Carozzo et al. has shown that the largest interaction between a water molecule and an amino acid zwitterion occurs at the carboxylate group, with hydrogen bonds forming between the carboxylate oxygen atoms and the hydrogens of water.[11] With the total negative charge of the carboxylate group reduced owing to the presence of the electron-withdrawing side chains, the attraction between the amino acid and the water molecule is not as great, resulting in lower solvation energies. Conversely, the methyl group of alanine donates its electrons to the amino acid backbone, increasing the attraction of water to the zwitterion relative to glycine. These conclusions are consistent with the estimated energies of solvation reported in Table IV.

The experimental proton affinities determined from mass spectrometry for the neutral glycine and alanine molecules in the gas phase, 208.2 and 212.2 kcal/mol,[24] respectively, are consistent with the calculated values of 222.3 and 225.8 kcal/mol, respectively (see Table V). Again, the inductive effect of the side chain is expected to affect the proton affinity. The electron-donating methyl group of alanine makes the nitrogen atoms more attractive to the proton, resulting in a more stable protonated species. The electron-withdrawing groups of the side chains of serine, cysteine, and threonine have the opposite effect by decreasing the basicity of the amino acid relative to that of glycine, as indicated by the results in Table V. Unfortunately, no experimental values are available for comparison. The equilibrium distance between the approaching proton and the nitrogen atoms for each of the amino acids studied (see Table V) is nearly equal to the standard N–H bond length of 1.01 Å.[17] This suggests that there exists an equal charge density distribution over the three N–H bonds of the protonated amine group.

Debies and Rabalais, using photoelectron spectroscopy, have determined the first vertical ionization potentials of glycine and alanine to be 10.0 and 9.8 eV,[25] respectively; the directly calculated ionization potentials for these amino acids, 8.61 and 8.46 eV, respectively, are therefore in error by about 14%. The ionization potentials calculated using Koopmans' theorem and the "8% rule", 10.15 and 10.09 eV, respectively, however, agree within 3% of the experimental values. Thus, the ionization potentials for the other amino acids are expected to be most reliably predicted by using Koopmans' theorem, i.e., 10.33, 9.47, and 10.23 eV, for serine, cysteine, and threonine, respectively. No experimental values for these amino acids are currently available for comparison. Mulliken population analyses of the singly positive amino acids showed that the ionized electron originated from the amine group of all of the amino acids with the exception of cysteine, where it originated from the sulfhydral group. These results are consistent with the conclusions of Debies and Rabalais who found that the most loosely bound electrons of glycine and alanine are those of the nonbonding nitrogen orbital.[25]

The zwitterions of the amino acids are expected to have a much larger dipole moment than the neutral species. This was the case for each amino acid studied (see Table I). As the experimental dipole moments of the gaseous amino acids have not been reliably determined, a comparison here is difficult. One report suggests that the experimental dipole moment of glycine in the gas phase is actually determined by a mixture of at least two conformations of glycine.[19] The reasoning here is based on the small barriers to rotation in the neutral species (for some examples, see Table III). In addition, since the dipole moments appear to be highly basis set dependent, comparison among the other computational methods is equally difficult. Thus, the gas-phase dipole moments of the amino acids must still be regarded as highly uncertain.

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