Structure and Stability of Complexes of Glycine and Glycine Methyl Analogues with H^+, Li^+, and Na^+

Frank Jensen

Contribution from the Department of Chemistry, Odense University, DK-5230 Odense M., Denmark. *Received May 8, 1992*

Abstract: The gas-phase structures of complexes of glycine and glycine methyl analogues with H^+, Li^+, and Na^+ have been investigated by ab initio calculations. Geometries have been optimized at the Hartree-Fock level with the 6-31G* basis set and relative energies determined with the MP2/6-31G* method. Higher level calculations showed that relative energies are rather insensitive to enlargement of the basis set and further inclusion of electron correlation, but the semiempirical MNDO method is of insufficient accuracy for being useful. A total of nine structures for protonated glycine are found, three corresponding to N-protonation and six corresponding to O-protonation. Thirteen structures of glycine-Li^+ have been optimized, and the lowest energy species corresponds to a five-membered ring in which lithium is coordinated to both nitrogen and oxygen in the neutral form of the amino acid. Four other structures are within ~10 kcal/mol of the global minimum. The lowest energy Na^+ complex is the same as that for Li^+, although species in which sodium is coordinated to both oxygens are only slightly higher in energy. For the low energy lithium complexes, the effect of substituting a hydrogen with a methyl either at C, O, or N was probed. Both N- and C-methylation stabilize preferentially the doubly oxygen coordinated form.

Introduction

The sequencing of peptides by mass spectrometrical methods has recently attracted much attention. One of the new approaches for obtaining structural information is the use of metal complexes of the sample for analysis.[1] In order to rationalize the ion fragmentation, it is desirable to have some information regarding the geometry of the complex. A detailed knowledge of the complexation modes in the gas-phase is also required before attempting condensed-phase modeling by theoretical techniques. The present paper examines possible structure and relative energies of complexes of the simplest amino acid, glycine, with H^+, Li^+, and Na^+.

The conformational space of glycine has been investigated by theoretical methods several times. The most recent and thorough study is that of Jensen and Gordon, in which a comparison between different semiempirical and ab initio methods is performed.[2] The highest level employed in this study was MP2/6-31G* single point calculations on HF/6-31G* optimized geometries. A total of eight structures corresponding to minima on the potential energy surface (PES) were found, together with 16 connecting transition structures. The conclusion was that semiempirical or low level ab initio methods are not accurate enough for obtaining reliable information regarding the PES, but inclusion of electron correlation apparently had little effect on relative energies.

Prior to this work there had not been any reports of ab initio calculations on amino acid-metal complexes; however, just prior to submission of the present paper, Bouchonnet and Hoppilliard published calculations of glycine proton and sodium affinities.[3] They employed the MP2/6-31G*//HF/3-21G method, which is a slightly lower level of theory than used in this paper. We have also employed a more systematic search for possible energy minima, e.g., Bouchonnet and Hoppilliard found a total of three structures corresponding to protonated glycine and five complexes with sodium, compared to the nine protonated species and 13 sodium structures reported below.

In the present work we have used the word "structure" to indicate a molecular geometry which represents a minimum on the PES. Thus, several structures can have the same atomic bonding (although this distinction becomes blurred when dealing with metal complexes) and differ only in a conformational sense.

Table I. Relative Energies (in kcal/mol) of Protonated Glycine Structures

structure	HF/6-31G*	MP2/6-31G*[a]	ΔZPE
H1	0.0	0.0	0.0
H2	4.6	3.7	0.0
H3	10.8	10.1	-0.3
H4	13.8	17.6	-1.2
H5	19.1	22.5	-1.2
H6	26.5	32.7	-2.2
H7	27.1	33.2	-2.0
H8	30.2	36.7	-2.4
H9	31.6	38.1	-2.3

[a] On HF/6-31G* optimized geometries.

Experimental works often focus on structures exhibiting different chemistry; each of these structures may be a mixture of several conformations. We have chosen to divide the minima on the PES into "groups" which have the same mode of complexation; these groups correspond approximately to the concept of structures often used by experimentalists.

Computational Methods

A description of notation and procedures used in this paper can be found in ref 4. All geometries have been optimized at the HF/6-31G* level without any symmetry constraints, using the GAMESS program package.[5] The optimizations were, in general, started from nonsymmetric geometries, which should ensure that only genuine minima are located. All the protonated glycine minima were characterized by frequency calculations, but only a few selected metal structures (indicated in the text below) have been characterized in this fashion. Improved estimates of relative energies have been obtained by performing calculations at the MP2/6-31G*//HF/6-31G* level, and only the MP2 results are discussed in this paper. Calculations at the MP4/6-31G* and MP2/6-31+G(2d) levels were also done for the five lowest energy structures of glycine-Li^+. MP calculations were done using the Gaussian90 program package,[6] and MNDO calculations have been performed with the MOPAC program package.[7] Only selected geometrical data and relative energies are given in the paper; full details regarding geometries and total energies are available from the author upon request.

(1) (a) Grese, R. P.; Cerny, R. L.; Gross, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 2835. (b) Leary, J. A.; Zhou, Z.; Ogden, S. A.; Williams, T. D. *J. Am. Soc. Mass Spectrom.* **1990**, *1*, 473. (c) Leary, J. A.; Williams, T. D.; Bott, G. *Rapid Commun. Mass Spectrom.* **1989**, *3*, 192. (d) Russell, D. H.; McGlohon, E. S.; Mallis, L. M. *Anal. Chem.* **1988**, *60*, 1818. (e) Mallis, L. M.; Russell, D. H. *Int. J. Mass Spectrom. Ion Proc.* **1987**, *78*, 147. (f) Mallis, L. M.; Russell, D. H. *Anal. Chem.* **1986**, *58*, 1076. (g) Adams, J.; Gross, M. L. *Anal. Chem.* **1987**, *59*, 1576. (h) Tang, X.; Ens, W.; Standing, K. G.; Westmore, J. B. *Anal. Chem.* **1988**, *60*, 1791.

(2) Jensen, J. H.; Gordon, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 7917.

(3) Bouchonnet, S.; Hoppilliard, Y. *Org. Mass Spectrom.* **1992**, *27*, 71.

(4) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.

(5) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Jensen, J. H.; Koseki, S.; Gordon, M. S.; Nguyen, K. A.; Windus, T. L.; Elbert, S. GAMESS; *QCPE Bull.* **1990**, *10*, 52.

(6) Frisch, M. J.; Head-Gordon, M.; Tucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzales, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. *Gaussian90*, Gaussian, Inc.: Pittsburgh, PA, 1990.

(7) Stewart, J. J. P. MOPAC v6.0; *QCPE Bull.* **1990**, *10*, 86.

0002-7863/92/1514-9533$03.00/0

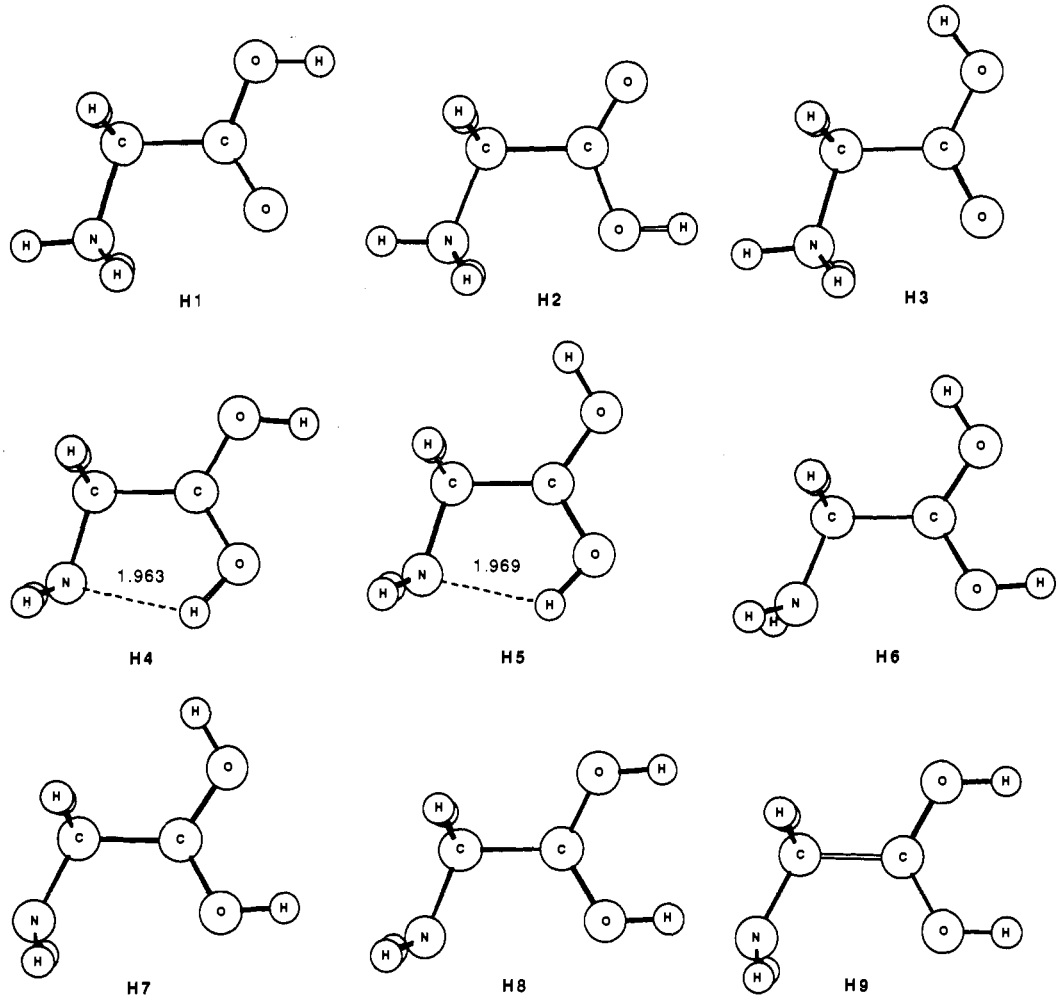

Figure 1. Optimized geometries for protonated glycine. Distances in angstroms.

Results and Discussion

A systematic search for minima for protonated glycine as performed by optimizing starting structures having N–C–C–O torsional angles of 10° and 170°, combined with rotational freedom of the amino/ammonia group and OH groups. Optimization revealed a total of nine minima on the PES, of which eight have C_s symmetry. All of these were characterized by frequency calculations as being genuine minima (i.e., having no imaginary frequencies). Three of these are N-protonated and correspond to combinations having the ammonia group and the carboxyl hydrogen either syn or anti to the carbonyl oxygen. Drawings of these structures are shown in Figure 1 as H1–3, and relative energies are given in Table I. The other six minima are O-protonated and correspond to combinations of the oxygen protons being either syn or anti to the amino group. When the hydroxy proton near the amino group is anti, minima exist both for the nitrogen lone pair syn and anti to the oxygen. These structures are represented by H4–9 in Figure 1. The only minima not possessing C_s symmetry at the HF/6-31G* level is that of H6. However, the corresponding C_s structure is only 0.002 kcal/mol higher in energy and has an imaginary frequency of only $35i$ cm^{-1}; thus the PES is very flat in this region, and H6 may possibly have C_s symmetry at higher levels of theory.

As expected,[8] the N-protonated structures H1–3 are the most stable, and H1 with the ammonia group syn to the carbonyl oxygen is calculated to be 3.7 kcal/mol more stable than the anti conformation. The two O-protonated conformations H4 and H5 are relatively low in energy, 17.6 and 22.5 kcal/mol, respectively, due to the hydrogen bonding between the anti hydroxyl hydrogen and the amino group (distances to the nitrogen are 1.96 and 1.97 Å). These energy differences do not include vibrational effects. Table I shows that inclusion of zero-point energies gives no qualitative changes. At the presently employed level of theory, it is likely that basis set and electron correlation inadequacies result in larger errors than neglect of vibrational effects; thus, for the metal complexes below we have not considered the effect of zero-point energies.

The H1–9 structures can be directly related to the C_s symmetric minima found by Jensen and Gordon.[2] For the N-protonated species, the stability order is conserved although the energy differences are somewhat larger than for the neutral system. The picture is less clear from the O-protonated glycines, since each can be formed from two different neutral conformations by protonation.

Suitable starting geometries for glycine–Li^+ complexes were generated from the protonated glycines by replacing all unique hydrogens with lithium. Any symmetry present was destroyed by rotating the lithium 10–15° out of the symmetry plane. Additional trial structures were generated by rotating dihedral angles selected by chemical intuition. After reoptimization, a total of 13 minima were found on the PES, and they are shown in Figure 2 as M1–2 and M4–14. M3 is a separate minimum only when the metal is sodium, as explained below.

The 13 structures can be classified into five groups distinguished by the mode of metal coordination. *Li*1, *Li*4, and *Li*5 all have 5-membered rings with lithium coordinated to both nitrogen and oxygen and can be thought of as arising from complexation of Li^+ with the neutral form of glycine. The ring is slightly envelope-shaped, analogous to cyclopentane, and the energy cost for achieving a planar conformation is very small, e.g., for Li1 the C_s-symmetric structure is 0.006 kcal/mol higher in energy.[9] Li1

(8) The experimental proton affinity of methylamine is 20.4 kcal/mol higher than that of ethyl acetate (Meot-Ner, M.; Sieck, L. W. *J. Am. Chem. Soc.* **1991**, *113*, 4448), a value similar to the 17.6 kcal/mol energy difference between the lowest energy N- and O-protonated isomers of glycine.

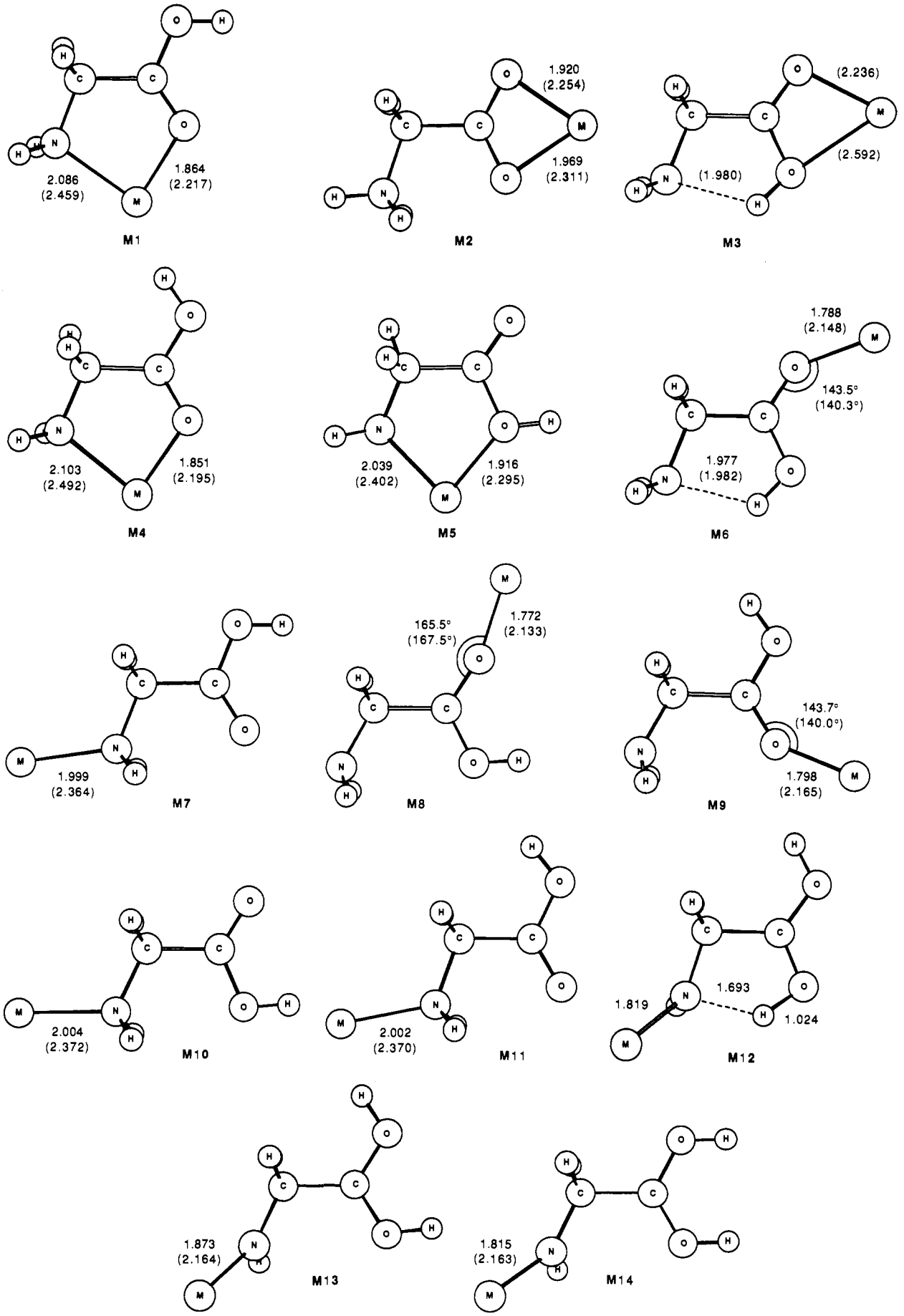

Figure 2. Optimized geometries for glycine–M^+ complexes (M = Li, Na). Distances in angstroms, angles in degrees, values for M = Na in parentheses.

Table II. Relative Energies (in kcal/mol) of M^+–Glycine Complexes

	MNDO		HF/6-31G*		MP2/6-31G*[a]	
structure	Li	Na	Li	Na	Li	Na
M1	0.0	0.0	0.0	0.0	0.0	0.0
M2	39.3	41.2	9.4	7.7	4.1	2.2
M3	12.2	*b*	*b*	6.1	*b*	4.7
M4	5.3	1.2	7.6	7.4	7.1	7.0
M5	8.2	6.8	12.6	11.1	9.3	8.2
M6	10.4	1.5	11.0	5.8	11.8	5.7
M7	22.2	8.1	24.0	17.3	22.3	15.1
M8	14.0	3.8	20.4	14.4	23.3	16.4
M9	17.1	5.2	21.7	15.7	24.2	17.2
M10	23.1	9.1	27.7	20.8	25.5	18.1
M11	20.5	14.5	34.2	27.3	31.9	24.4
M12	51.6	53.7	68.1	*c*	63.6	*c*
M13	47.8	34.6	79.5	82.8	80.8	118.5
M14	52.8	*d*	85.4	89.2	87.0	125.3

[a] On HF/6-31G* optimized geometries. [b] No minimum, optimization leads to M6 structure. [c] Optimization leads to Na11 structure. [d] No Na14 structure could be found.

Table III. Relative Energies (in kcal/mol) of Li^+–Glycine Complexes

structure	MP2/ 6-31G*	MP3/ 6-31G*	MP4/ 6-31G*	MP2/ 6-31+G(2d)
Li1	0.0	0.0	0.0	0.0
Li2	4.1	6.9	4.4	3.0
Li4	7.1	7.2	7.0	5.9
Li5	9.3	10.3	9.4	10.0
Li6	11.8	11.7	11.9	9.3

and Li4 differ only in the conformation of the hydroxyl group, while Li5 is protonated on the same oxygen as is coordinated to lithium. The second lowest structure in terms of energy is the C_s-symmetric Li2, in which lithium is coordinated to both oxygens, i.e., complexation to the zwitterionic form of glycine. The third group consists of Li6, Li8, and Li9, all having C_s symmetry, where lithium is coordinated only to the carbonyl oxygen. These structures are analogous to H4 and H7. Apparently the angle bend potential for the C–O–Li angle is so soft that there do not exist separate minima corresponding to H5 and H9. Furthermore, lithium compex analogues of H6 and H8 (i.e., nitrogen inversion on Li8 and Li9) are not minima but transition structures, as proven by frequency calculations. The last two groups have lithium coordinated only to nitrogen. Li7, Li10, and Li11 all have C_s symmetry and are lithium analogues of the N-protonated glycines H1–3. Finally, the last three, Li12–14, represent structures corresponding to N-lithiated O-protonated glycine. All of these have C_1 symmetry with a Li–N–C–C dihedral angle close to 120°. A potential fourth conformation in this series with hydroxyl groups anti and syn (with respect to the CH_2 group) does not represent a minimum on the PES; upon optimization it collapses to Li7. On the HF/6-31G* surface, Li12 is a genuine minimum; however, the long O–H bond of 1.02 Å (compared to 0.96 Å for Li13) and the very short N–H distance of 1.69 Å (compared to 1.98 Å for Li6) suggest that Li12 may possibly collapse to Li11 at better theoretical levels.

Relative energies at the MP2/6-31G* level of the 13 structures are given in Table II, and additional data for Li–16 at higher levels of theory are in Table III. From Table III it is seen that inclusion of electron correlation beyond MP2 has very little effect. The MP4 results are essentially identical to the MP2 data. Expanding the basis set to 6-31+G(2d) (i.e., adding a diffuse and a polarization function) also has a rather modest effect with changes being less than 2 kcal/mol. Note, however, that the results with the better basis set indicate that Li6 is slightly more stable than Li5.

Of the 13 lithium structures listed in Table II, only the first five are expected to be of chemical significance under normal gas-phase conditions, such as in a mass-spectrometrical experiment. These five complexes are not unexpectedly the four with double lithium coordination and Li6, which is stabilized by intramolecular hydrogen bonding (distance is 1.98 Å). Notice that the five low-energy structures represent three different modes of complexation.

Using the 13 glycine–Li^+ complexes as templates, we then optimized the corresponding Na^+ species, which resulted in 12 unique sodium complexes. The structure corresponding to Na12 apparently does not represent a minimum on the sodium PES; minimization produces instead Na11. An additional structure with complexation of Na^+ to the neutral form of glycine (Na3) was also found. A corresponding Li3 species does not exist; upon optimization it returns to the open form Li6. The overall geometries of the sodium complexes are very similar to those of lithium except for the distances involving sodium (see Figure 2). Relative energies of the sodium complexes are given in Table II.

The chemically most significant difference between the sodium and lithium species is that the monocoordinated complexes M6–11 are ~7 kcal/mol better stabilized by sodium than by lithium relative to the doubly coordinated M1–5. Na6 is calculated to be the fourth lowest energy structure, being only 5.7 kcal/mol above the global minimum. The data in Table III suggest that better basis sets may further lower this value. Also, the zwitterionic salt Na2 is now very close in energy to Na1. The metalated structures M13 and M14 are, as expected, destabilized by replacement of sodium for lithium.

MNDO calculations have previously been used for addressing the most stable configurations of complexes of Li^+ and Gly-Gly-Gly;[1a] however, the data in Table II clearly show that the semiempirical method is of dubious accuracy. Especially the stability of the carboxylate salt M2 is severely underestimated, and the energy differences between the sodium complexes are too small at the MNDO level.

The calculations by Bouchonnet and Hoppilliard located three energy minima for protonated glycine, which correspond to our structures H1, H2, and H4, and their five sodium complexes are Na1–3, Na5, and Na9.[3] There are some differences in geometry due to the better basis set used by us in the optimization, e.g., the ammonia group in H1 and H2 optimized at the HF/6-31G* level is rotated 60° relative to the structures obtained with the 3-21G basis.[3,10] Na9 has a doubly oxygen-coordinated form with the 3-21G basis set (Na–O distances of 2.23 and 2.33 Å),[4] while it is monocoordinated as shown in Figure 2 with the 6-31G* basis set (Na–O distances of 2.19 and 4.25 Å). Na3 also becomes more asymmetric with the better basis but retains its bis-coordination (Na–OH distance increases from 2.28 to 2.59 Å). Note that the open form Na6 geometrically is quite close and is only 1 kcal/mol higher in energy;[11] thus it is possible that these two structures merge at higher levels of theory.

In order to extend the scope of the present investigation, we have also for Li1–6 tested the effect of replacing a hydrogen with a methyl group on either carbon, nitrogen, or oxygen. Introducing a methyl group on carbon converts glycine to alanine, while the other substitutions produce sarcosine and the methyl ester of glycine. The optimized geometries are very similar to those given in Figure 2, with maximum deviations being less than 0.02 Å in bond lengths and a few degrees in bond angles. For the methyl ester, a structure corresponding to Li2 is not possible, while for the sarcosine analogue of Li2 two different conformations are possible, in which the lowest energy species has C_s symmetry while the other is without symmetry. Relative energies are given in Table IV.

The difference in stability between the glycine and alanine complexes is minor, but note that Li2 becomes stabilized relative to Li1 by 2.4 kcal/mol upon going to alanine. The stability order

(9) Bouchonnet and Hoppilliard (ref 3) report that Na1 and Na4 are planar at the HF/3-21G level.

(10) The structure corresponding to H1 found by Bouchonnet and Hoppilliard (ref 3) has one imaginary frequency at the HF/6-31G* level, while the H1 geometry shown in Figure 1 is a genuine minimum.

(11) Both Na3 and Na6 are minima on the PES, as proven by frequency calculations. The lowest frequencies are 53 and 43 cm^{-1} (both of a' symmetry), respectively, indicating that interconversion between these isomers should be very facile.

Table IV. Relative Energies (in kcal/mol) of Li^+–Glycine Methyl Analogue Complexes

CH_3 position	structure	HF/6-31G*	MP2/6-31G*[a]
C–CH_3	Li1	0.0	0.0
	Li2	7.0	1.7
	Li4	8.1	7.6
	Li5	11.7	8.4
	Li6	11.4	12.1
O–CH_3	Li1	0.0	0.0
	Li2		
	Li4	9.5	8.8
	Li5	13.5	10.2
	Li6	22.5	24.3
N–CH_3	Li1	0.0	0.0
	Li2	2.2[b]	−3.3[b]
		2.1[c]	−2.4[c]
	Li4	7.4	7.0
	Li5	12.2	8.9
	Li6	10.3	11.0

[a] On HF/6-31G* optimized geometries. [b] C_s symmetric structure. [c] C_1 symmetric structure.

is also unchanged in the methyl ester series, and Li6 is significantly destabilized by the steric interaction of the methyl group with the amino moiety. The optimized geometry has a N–C–C–O dihedral angle of 65°, in contast to 0° for the unmethylated case. The alternative conformation of this complex, corresponding to Li8, is 23.4 kcal/mol above Li1. Introducing a methyl group at nitrogen lowers the energy of Li2 by 7 kcal/mol relative to Li1, while the effect on the other structures is minor. The preferential stabilization of Li2 over Li1 in sarcosine was somewhat unexpected; one might a priori have predicted the reverse effect by arguing that the electron-donating effect of a methyl group would preferentially stabilize the structure where the positively charged metal atom was closest to the amino group, i.e., Li1.

As substitution at the α-carbon and enlarging the basis set both tend to favor the M2 structure over M1, it is likely that M2 is lowest in energy for the larger amino acids, although the energy difference probably is only a few kcal/mol. For the larger alkali metal ions, mono-oxygen-coordinated species like M6 may also become close in energy to M1 and M2; at least the substitution of sodium for lithium seems to favor this structure. For some amino acids, and especially for peptides and proteins, additional modes of complexation (e.g., tri and tetra coordination to the metal[12]) probably also become important.

In order to obtain absolute values of protonation and metalation for glycine and its methyl analogues, additional calculations for protonated glycine methyl analogues and the corresponding neutral forms were performed. The most stable conformation of glycine has been given by Jensen and Gordon,[2] and we have assumed that the global minimum for the glycine methyl analogues could be obtained by simply replacing the appropriate hydrogen with a methyl group followed by reoptimization of the geometry. Similarly, the protonated glycine methyl analogues were constructed by hydrogen replacement on the protonated glycines H1 and H2. The global minimum for the sodium complexes of glycine methyl analogues were assumed to be the most stable of those resulting from Na1 and Na2. For the lithium complexes, Li2 is the most stable sarcosine structure, while Li1 still is favored with alanine. When sodium is the complexing cation, Na2 is in both cases the lowest energy species.[13]

In addition to the MP2/6-31G* calculation, we have also employed the 6-31+G(2d) basis; results are given in Table V. The calculated energy difference between glycine and protonated glycine with the largest basis set is 215.0 kcal/mol, and inclusion of enthalpy corrections at T = 298 K based on harmonic frequencies brings the value down to 206.0 kcal/mol. Locke and McIver have reported an experimental proton affinity of 213.0 kcal/mol for glycine,[14] while a more recent study by Gorman et al. gave a value of 205.7 ± 1.7 kcal/mol.[15] It is quite likely that the good agreement to a certain extent is fortuitous, with errors from an incomplete basis set and incomplete inclusion of electron correlation canceling. The experimental proton affinity order glycine < alanine < glycine methyl ester < sarcosine, however, is reproduced, although glycine methyl ester and alanine have almost the same calculated affinity. The calculations indicate that the same order should be valid for the Li^+ and Na^+ complexes. This is also observed experimentally for the sodium complexes, while sarcosine and glycine methyl ester have been interchanged for the lithium species.[16] This inconsistency is most likely due to basis set limitations, although the neglect of zero-point energies and entropy contributions, which are included in the experimental data, may also have an effect.

Table V. Absolute Glycine Complexation Energies (in kcal/mol) Calculated at the MP2 level[a]

	H^+[b]		Li^+		Na^+	
substitutent	A	B	A	B	A	B
none	222.7	215.0	66.4	58.4	46.0	38.5
C–CH_3	226.4	218.6	67.7	59.7	47.5	40.5
O–CH_3	226.1	218.8	69.6	62.0	48.6	41.4
N–CH_3	230.3	223.1	69.4	63.0	50.8	44.8

[a] Basis set A is 6-31G*, B is 6-31+G(2d). [b] Reported experimental values are 213.0, 215.8, 216.8, and 219.4 kcal/mol, respectively, ref 14. More recent results have given values of 205.7 ± 1.7 and 212.8 ± 1.3 kcal/mol for glycine and alanine, see ref 15.

Conclusion

Calculations at the RHF/6-31G* level have shown that nine minima, all of which have essentially C_s symmetry, are present on the PES for gas-phase protonated glycine. The lowest energy structure corresponds to N-protonation of the lowest energy form of neutral glycine. Complexation of Li^+ and Na^+ with glycine gives five classes of coordination which, after addition of conformational freedom, produces 13 minima. The five classes consist of structures having metal coordination to both nitrogen and oxygen, to both oxygens, to only the carbonyl oxygen, and to only nitrogen in the sense of addition to the lone pair, and finally structures corresponding to direct metalation of the amino group. For glycine itself, a five-membered ring structure with N- and O-coordination is predicted to be the lowest energy species, but one corresponding to the metal salt of the zwitterionic form is only a few kcal/mol higher in energy. A total of five Li^+ and six Na^+ species are within ~10 kcal/mol of the global minimum, of which three have the five-membered ring geometry, while the other are either mono- or bis-oxygen coordinated.

The bis-oxygen coordinated structure is preferentially stabilized by larger basis sets, by changing the metal from lithium to sodium, and by substituting a methyl group for hydrogen either at carbon (forming alanine) or at nitrogen (forming sarcosine). For glycine and its methyl analogues, the absolute energies of protonation compare favorably with experimental values, and the stability order observed for the proton is calculated to be preserved for the lithium and sodium complexes.

Perhaps the most significant outcome of the present work is the fact that several structures with different complexation modes are very close in energy, even for the simplest amino acids.[1a] For peptides this means that a number of possible modes of complexation must be considered, and unfortunately it does not appear that semiempirical calculation are of sufficient accuracy for distinguishing between such isomers.

Acknowledgment. This work was supported by the Danish Natural Science Research Council (Grant Nos. 11-9276 and 11-9686).

(12) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353.

(13) For alanine, Na1 is 1.5 kcal/mol higher in energy than Na2, while for sarcosine, Na1 is 6.5 kcal/mol above Na2 at the MP2/6-31+G(2d) level.

(14) Locke, M. J.; McIver, R. T., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 4226.

(15) Gorman, G. S.; Speir, J. P.; Turner, C. A.; Amster, I. J. *J. Am. Chem. Soc.* **1992**, *114*, 3986.

(16) Bojesen, G.; Breindahl, T.; Andersen, U. N., submitted for publication.