Salt Bridge Structures in the Absence of Solvent? The Case for the Oligoglycines

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Abstract: Protonated and sodiated oligoglycines, Gly_n ($n = 1-6$), were generated in the gas phase using matrix-assisted laser desorption ionization and their structure probed by measuring collision cross sections in helium. It was found that the sodiated oligoglycines have larger cross sections than the protonated forms and that the difference between the cross sections of the two forms increases with increasing oligoglycine size ($n = 2-5$) reaching a value of >11% for pentaglycine. This observation indicated that the protonated forms are more compact and spherical than the sodiated species. Theoretical studies including ab initio MP2, density functional theory, and molecular mechanics calculations indicated that protonated oligoglycines assume almost spherical shapes. The same was true for sodiated forms if it was assumed that the sodium ion was bound to a zwitterion oligoglycine structure via a salt bridge system. However, structures obtained when the sodium ion was solvated by nonzwitterionic oligoglycines were fairly extended with strongly oblate shapes. Cross sections calculated for these latter structures agreed well with the experimental data of the sodiated species, while cross sections calculated for the spherical shapes agreed well with the experimental data of the protonated forms. Relative energies obtained from calculations (B3LYP/6-311++G**) on Gly_nNa^+ ($n = 1-4$) indicated that the salt bridge forms are less stable than the charge solvation forms by 3, 14, 8, and 8 kcal/mol for $n =$ 1, 2, 3, and 4, respectively. Both theory and experiment indicated that sodiated oligoglycines do not form salt bridge structures in the gas phase.

Introduction

Naturally occurring amino acids are very important building blocks of a large variety of biological substances such as antibodies, enzymes, and proteins making up the framework of cells and tissues. These molecules are carboxylic acids with an amino group in α-position, $H_2N-CHR-COOH$. However, certain properties, both physical and chemical, are not consistent with such a structure. In contrast to amines and carboxylic acids, amino acids are nonvolatile crystalline solids which melt with decomposition at fairly high temperatures. Their dipole moments measured in aqueous solution are unusually high and their acidity and basicity constants are many orders of magnitudes lower than expected for $-COOH$ and $-NH_2$ groups.[1] All these observations are consistent with a zwitterion structure, $H_3N^+-CHR-COO^-$. However, the situation is different in the absence of the intermolecular interactions prevalent in the condensed phase. For instance, it has been shown experimentally[2] and theoretically[3] that glycine is not a zwitterion if isolated as a single molecule in the gas phase. However, for charged particles such as protonated or sodiated amino acids or peptides it has been suggested that the addition of an extra charge could stabilize a zwitterion structure via an intramolecular salt bridge system in certain favorable cases.[4−6] For instance, there is some indirect evidence that singly protonated bradykinin, a nonapeptide containing two very basic argenine residues, is protonated on both guanidino groups while the acidic C-terminus is deprotonated in the most stable gas-phase structure.[6] A thorough study on protonated oligoglycines, on the other hand, showed that these species are not zwitterions, while preliminary data on sodiated oligoglycines indicate that some of these species might be.[4,5] The problem with all these studies to date is that experimental methods are limited to techniques such as H/D-exchange reactions,[4,5] dissociation of proton-bound dimers, and thermal or collision-induced dissociation,[6,7] which all probe transition states between reactants and products that do not necessarily resemble the thermal equilibrium geometries of the unperturbed peptide ions. In addition these studies strongly rely on theoretical calculations, ab initio for smaller and semiempirical for larger systems, in support of the experimental results. Since the two structural forms, salt bridge and nonzwitterion charge solvation, are such different species, their relative energies obtained at any level of theory feasable for these rather large systems necessarily have large uncertainties.

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(3) The potential surface of glycine has extensively been researched theoretically. Some of the relevant studies include: Oegerle, W. R.; Sabin, J. R. *J. Mol. Struct.* **1973**, *15*, 131. Tse, Y.-C.; Newton, M. D.; Vishveshwara, S.; Pople, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 4329. Yu, D.; Armstrong, D. A.; Rauk, A. *Can. J. Chem.* **1992**, *70*, 1762. Ding Y.; Krogh-Jespersen K. *Chem. Phys. Lett.* **1992**, *199*, 261. Jensen, J. H.; Gordon, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 8159.

(4) Lee, S.-W.; Beauchamp, J. L. Private communication.

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Another approach to obtain structural information of ions in the gas phase is probing its geometry rather than its chemical properties using the ion mobility based ion chromatography technique.[8] This method has the definitive advantage that it samples ions in their equilibrium geometries under thermal conditions. While it also relies on theoretical calculations, they are only used to obtain model geometries rather than precise relative energies for different forms. Therefore, rather low-level calculations are perfectly appropriate for this purpose since geometries are much easier to accurately characterize than energies. However, the ion chromatography technique requires that two isomers have significantly different shapes and thus different mobilities and cross sections in order to be able to distinguish between the two. For this reason the technique was not able to answer the question whether protonated bradykinin forms a salt bridge in the gas phase, since calculations indicated that both forms are expected to have very similar cross sections, and both agreed with experiment.[9]

In this study we report ion mobility data for protonated and sodiated oligoglycines in an attempt to determine whether salt bridge structures are formed in the gas phase. These studies were stimulated by recent H/D-exchange results[4] that suggested some sodiated glycine oligomers have salt bridge forms and some do not. The oligoglycine systems are particularly well-suited for ion chromatography study because molecular mechanics calculations indicate that the sodiated charge solvation and the sodiated salt bridge forms assume very distinct geometries with the salt bridge tightly folded and the charge solvation quite extended. Thus, the experimental cross sections should be diagnostic of the structure of the sodiated species. The protonated species are also predicted to be compact by the calculations like the salt bridge, and comparison of their experimental cross sections with the sodiated glycines should also be diagnostically useful. Furthermore, the repetitive glycine (Gly) unit in these systems, Gly_n ($n = 1-6$), makes a systematic study of the size dependence possible. Such size dependences have proven very useful in the past to assign structural families, like for instance in the case of carbon clusters,[10,11] or to investigate charge solvation shells and dynamic effects, like in the case of poly(ethylene glycol)s.[12]

Experimental Section

Experimental details and instrumentation have been previously described.[12,13] Briefly, ions are formed by MALDI (matrix-assisted laser desorption ionization) using 2,5-dihydroxybenzoic acid as a matrix and an excimer laser running as a nitrogen laser at 100 Hz as a photon source. For this study the strongest ion signals were obtained with an unusually high sample-to-matrix ratio of ~1:100. Ions of interest were mass selected in a reverse geometry double focusing mass spectrometer. A packet of ions of 1−5 μs duration was injected at 10 eV (lab) into a drift cell filled with 3 Torr of helium and pulled through the cell by a weak electric field of 2.5−25 V/cm. The helium temperature was usually kept at 300 K except for a number of low-temperature experiments at 80 K. After exiting the drift cell the ions pass through a quadrupole mass filter and an arrival time distribution (ATD) is obtained at the detector.

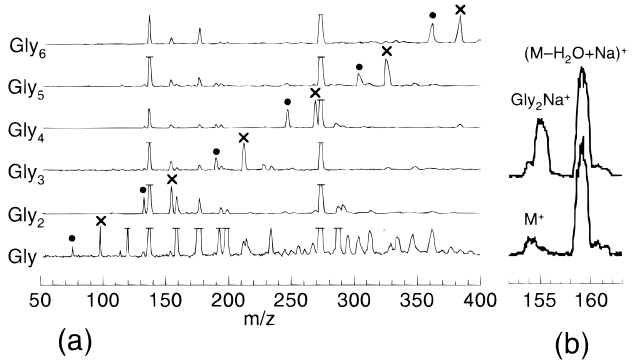

Figure 1. MALDI mass spectra of oligoglycines. (a) Spectra obtained for the six samples indicated on left. Peaks of interest are marked with ● for Gly_nH^+ and × for Gly_nNa^+. (b) Detail of Gly_2/matrix spectrum (top trace) in comparison with matrix-only spectrum (bottom trace). Matrix (M) used is 2,5-dihydroxybenzoic acid.

A large variety of different ions were observed in the mass range of interest, most of which are some sort of clusters of matrix molecules and fragments thereof, both protonated and sodiated. The two Gly_nH^+ and Gly_nNa^+ ion peaks of interest in the mass spectrum for a given n were often just a few percent as intense as the strongest matrix peaks. Examples are given in Figure 1. Due to possible impurity problems, extra care was taken to identify the ions of interest by their mass, by comparing mass spectra with and without sample added, and sometimes by their MI/CID (metastable ion/collision-induced dissociation) spectra. For instance, for $GlyH^+$ we observed the two major fragments with $m/z = 30$ ($NH_2CH_2^+$) and 48 ($NH_2CH_2OH_2^+$), which have previously been reported as MI and CID products.[14] Sodiated ions are readily identified as such by observation of the $m/z = 23$ fragment ion (Na^+).[15]

Signal levels after the drift cell were typically <1 count per laser shot. Therefore, to get a reasonable ATD, accumulation over tens or hundreds of thousands of laser shots was required.

Computational Methods

The simulated annealing procedure to generate candidate structures by molecular mechanics has been described previously.[9] Briefly, using the AMBER suit of programs[16] a starting conformation is subjected to 30 ps of dynamics at 800 K, then cooled to 100 K during a time period of 10 ps, and from there geometry optimized by minimizing its energy. This first candidate structure is then used as new input conformation and subjected to the same annealing sequence. In this fashion 100 candidate structures are generated in an attempt to cover reasonable conformations for a given system. Their cross sections are plotted versus their relative energies to generate a scatter plot. Conformations within 5 kcal/mol of the lowest energy conformation were considered reasonable models. For instance, for protonated pentaglycine we found 28 different conformers (out of 100 attempts) spread over an energy range of about 15 kcal/mol, 9 of them within the lowest 5 kcal/mol range. Thus each conformation was found more than 3 times in average. However, the low-energy conformations were located much more frequently, for instance, the one with the lowest energy 25 times. The scatter plot for this system is given in Figure 2.

For each reasonable model structure an orientation averaged projection cross section was calculated[10,17] for comparison with experimental data (see Appendix). Some of these structures were also employed as input for higher level calculations, ab initio and density functional theory (DFT), to get relative energies of salt bridge and charge solvation isomers of sodiated species. Ab initio Hartree−Fock calculations were

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(17) Wyttenbach, T.; von Helden G.; Batka, J. J. Jr.; Carlat, D.; Bowers, M. T. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 275.

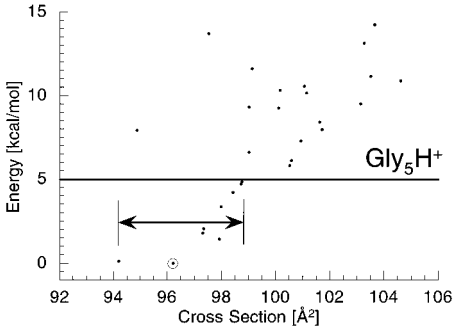

Figure 2. Scatter plot of energy versus cross section for protonated pentaglycine model structures obtained by molecular mechanics. The cross section range indicated by the arrow covers structures within 5 kcal/mol of the lowest energy structure (see Figure 4c), which is marked with a circle.

carried out including the Møller−Plesset correlation energy correction, truncated at second order (MP2). Exchange and correlation functionals in DFT computations were calculated by Becke's *Three Parameter Hybrid Method* including the LYP (Lee, Yang, Parr) expression (B3LYP).[18] Relative energies were in general obtained from fully optimized geometries and systematically studied as a function of basis set ranging from 6-31G to 6-311++G**. The program used for these studies was Gaussian 94.[19]

Results

At room temperature the arrival time distributions (ATDs) of all ions included in this study show one peak[20] with a width that appears to be nearly exclusively determined by the simple diffusion of the ion cloud in the drift cell. The ATDs obtained at 80 K are narrower than those at 300 K by a factor of ∼(80/300)$^{1/2}$ as expected by kinetic theory.[21] Cross sections obtained from ATDs of protonated and sodiated glycine oligomers are shown in Figure 3a. Cross sections increase monotonically as the oligomer size increases. The sodiated species are larger in all cases, varying from 3 to 4% for di- and triglycine to more than 11% for pentaglycine.

Cross sections calculated for model structures obtained from molecular dynamics simulations are given in Figure 3, parts b and c. All model structures within 5 kcal/mol of the lowest energy structure (shown as a filled symbol) are included and are the source for the error bars shown. The experimental cross sections are superimposed for comparison.

The lowest energy molecular mechanics structures were also used as starting points for both DFT and MP2 calculations. The optimized geometries obtained for both protonated and sodiated glycine using a 6-311++G** basis set and both MP2 and DFT (B3LYP) optimization agree well with those previously reported.[22,23] Relative energies for the different conformers are

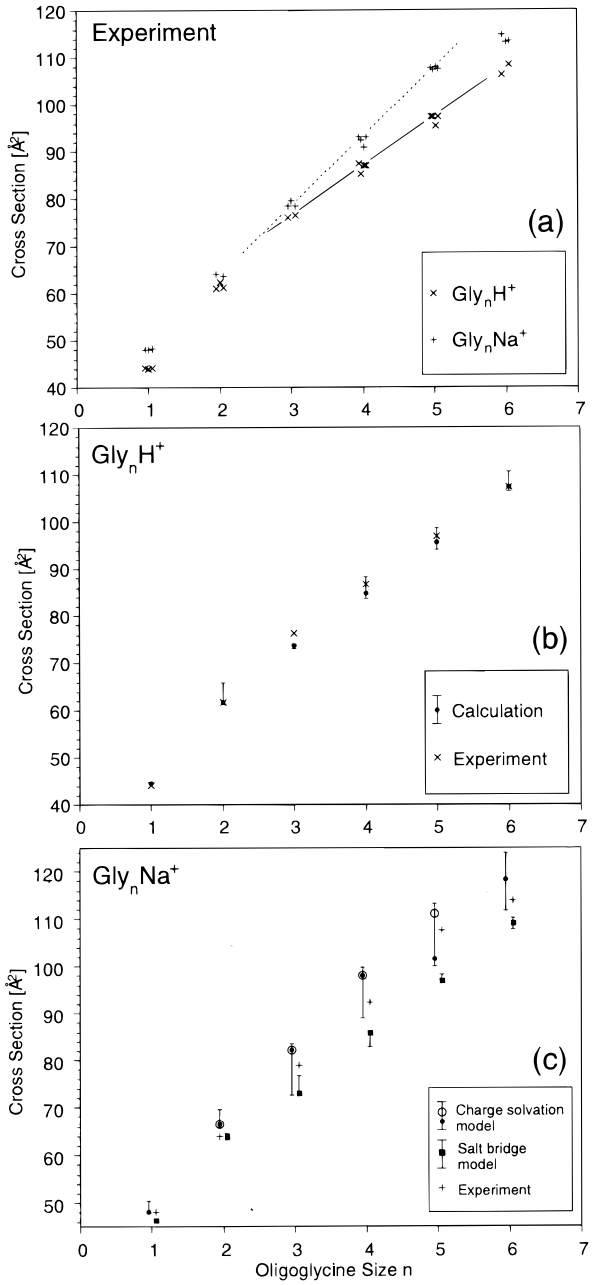

Figure 3. Cross sections of protonated and sodiated oligoglycines as a function of oligomer size: (a) experimental data and (b) calculated values for protonated, and (c) for sodiated model structures. The symbols are + and ×, experimental data; ● and ■, lowest energy model structures; and ○ unfolded low energy charge solvation structures as shown in Figure 4a. Bars indicate range covered by different conformers within 5 kcal/mol.

qualitatively also the same. However, the sodiated salt bridge structure is several kilocalories per mole less stable than the charge solvation form (see Table 1), while the two forms had similar energies in the previous lower level Hartree−Fock calculations.[22] The cross sections of the two forms are the same within a few percent and are in good agreement with experiment (Figure 3c). For sodiated diglycine the charge solvation form is clearly more stable than the salt bridge isomer (by >10 kcal/mol). The calculated cross sections for the two forms are again very similar, however, and both in good agreement with experiment.

As the systems get larger greater structural differences are predicted for the lowest energy structures of the charge solvation

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Table 1. Calculated Relative Energies (kcal/mol) of Gly_nNa^+ Salt Bridge Structures with Respect to the Corresponding Charge Solvation Forms as a Function of Basis Set Used (zero point energy (ZPE) corrections not included)

	E(salt bridge) − E(charge solvation)				
	method	6-31G	6-311+G*	6-311++G**	ZPE
$GlyNa^+$	MP2		−1.3	3.0	
	DFT	−1.3[a]	0.2	2.8	0.6[e]
Gly_2Na^+	DFT	9.5	10.8	13.7	0.7[f]
Gly_3Na^+	DFT	3.7[b]		∼8[c]	
Gly_4Na^+	DFT	4.5[b]		7−9[d]	

[a] 6-311G basis set used. [b] Geometry optimization of the salt bridge form yields a compact charge solvation structure (see Discussion). [c] Single point calculation at B3LYP/6-31G geometry. [d] Correction (3−4 kcal/mol) to 6-31G energy estimated on the basis of results of smaller systems. [e] Zero point energies calculated using B3LYP/6-311G. [f] Zero point energies calculated using B3LYP/6-31G.

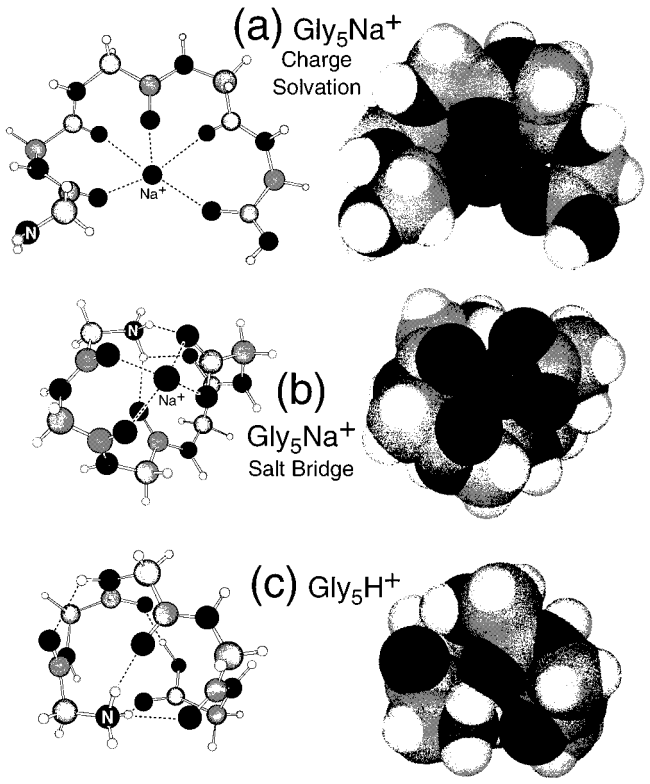


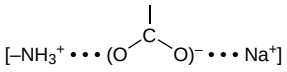
Figure 4. "Ball and stick" (left) and "space filling" (right) model structures (a) for sodiated pentaglycine in an unfolded charge solvation form, (b) in a compact salt bridge form, and (c) for protonated pentaglycine. N-terminus nitrogens are labeled with "N"; C-terminus carbons, with "C".

form and the salt bridge. An example is given in Figure 4 for pentaglycine. For Gly_nNa^+ ($n = 1-6$) up to n electrostatic Na−O bonds with carbonyl oxygens are observed among the low energy conformers for the charge solvation isomer. In fact, for $n = 1-4$ this type of structure represents *the* lowest energy conformation. The large coordination number causes the relatively small peptide to unfold and span around the sodium like an open umbrella (Figure 4a). This large degree of unfolding for these oblate, almost planar geometries is reflected in large collision cross sections (circles in Figure 3c). In contrast, the lowest energy conformations of the salt bridge structures (Figure 4b) and those of the protonated species (Figure 4c) are almost spherical and have much smaller cross sections (squares in Figure 3c, dots in 3b, respectively).

A number of sodiated tri- and tetraglycine structures obtained by molecular mechanics were used as input for DFT calculations in an attempt to determine relative energies of salt bridge and charge solvation forms for these larger oligoglycines. The results, summarized in Table 1, indicate that the charge solvation form is indeed lower in energy for these systems as well, although not by quite as much as for diglycine. It should be noted that both addition of polarization and diffuse functions as well as zero point energy corrections favor the unfolded charge solvation forms.

Discussion

Gas-phase H/D-exchange experiments of sodiated oligoglycines using ND_3 as the exchange reagent show an interesting pattern.[4] While for Gly_2Na^+ and Gly_3Na^+ only 1 hydrogen is rapidly replaced by deuterium (and two additional hydrogens slowly), for $GlyNa^+$, Gly_4Na^+, Gly_5Na^+, and Gly_6Na^+ three hydrogens are quickly exchanged. An intriguing explanation for this observation has been put forward by Lee and Beauchamp that the three rapid exchanges occur on the protonated N-terminus, while the one fast/two slow pattern is explained by one quickly exchanging −COOH hydrogen and two slowly exchanging $-NH_2$ hydrogens. This hypothesis is supported by the fact that the corresponding methyl esters, which have no acidic hydrogens and cannot form a salt bridge form, do not exchange at all under the conditions of their experiment. Furthermore, with the aid of simple molecular models it can be demonstrated that stabilization of a



salt bridge system is least feasable for Gly_2Na^+ and Gly_3Na^+, because bond and dihedral angles have to be substantially dislocated from their equilibrium positions in order for $-NH_3^+$ to get close to $-COO^-$. This is not the case for Gly_nNa^+, $n > 3$. On the other hand, H/D-exchange experiments really probe transition-state structures, not ground states. Further, they do so while coordinated to the exchange reagent. In small systems such as those described here this latter fact can have a dramatic effect on structural preference. Hence, the H/D-exchange results while very interesting do not necessarily yield information about ground-state structures.

Ion mobility experiments, on the other hand, are indeed a probe of average equilibrium geometries under thermal conditions. Therefore it is of interest to examine the ion mobility data carefully in an attempt to find any indications for the existence of salt bridges. The experimental data displayed in Figure 3a show no sharp discontinuities as a function of oligomer size, in particular not between the sodiated triglycine and tetraglycine, where a structural change is expected on the basis of the H/D-exchange results. However, what can be seen is that sodiated oligoglycines have larger cross sections than the corresponding protonated species, which is particularly obvious for pentaglycine. In addition the dependence of the cross section on the oligomer size n is different for Gly_nH^+ and Gly_nNa^+ in the limited size range $2 \le n \le 5$. The sodiated species show a stronger dependence of cross section on oligomer size (dotted line in Figure 3a), indicating that they are more open, less spherical, than the protonated species (solid line in Figure 3a). This observation is in good qualitative agreement with the molecular mechanics result, if it is assumed that the sodiated species are in a charge solvation rather than in a salt bridge form. Comparing calculated with experimental cross sections for the sodiated glycines (Figure 3c) elucidates this point even better. For sodiated tetra-, penta-, and hexaglycine,

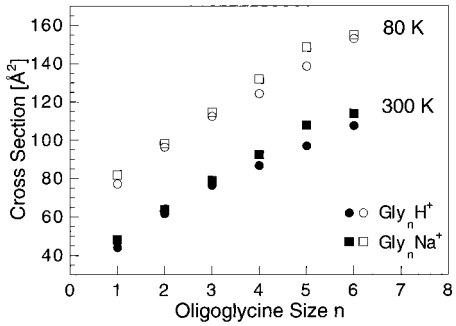


Figure 5. Cross sections for protonated and sodiated oligoglycines. ($n = 1-6$) at 80 K (top, open symbols) and 300 K (bottom, closed symbols). The symbols are □ and ■ for sodiated, and ○ and ● for protonated glycines.

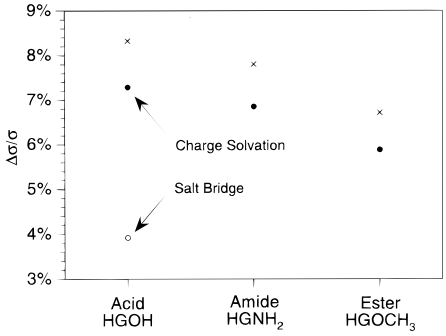


Figure 6. Difference between cross sections of sodiated and protonated species for glycine, glycine amide, and glycine methyl ester as observed experimentally (×) and calculated (●, ○) on the basis of geometry-optimized model structures.

cross sections of charge solvation structures agree significantly better with experiment than the salt bridge structures.[24] Furthermore, it appears certain for energetic reasons that sodiated diglycine assumes a charge solvation structure. If the calculated sodiated glycine data are anchored at the diglycine experimental result, then even better agreement is obtained between experiment and theory for the charge solvation structures and the salt bridge structures agree less well. Such a normalization process should remove any small systematic errors that might exist in the calculated cross sections.[25,26]

It is interesting that both the experimental and the lowest energy model cross sections for Gly_6Na^+ increase less than expected on the basis of the $n = 2-5$ result. This result indicates Gly_6Na^+ is somewhat more compact than the smaller oligomers. The molecular mechanics structure shows that only five out of six available >C═O groups are bound to the sodium ion in the lowest energy structure allowing a higher degree of folding of the peptide backbone. For Gly_5Na^+ the molecular mechanics result indicates that open (circle in Figure 3c) and somewhat more compact comformations (dot) have the same energy within 1.5 kcal/mol. To see if both structures were present in the 300 K experiments the cell was cooled to 80 K. The results are presented in Figure 5. Clearly the 80 K results exactly mirror the 300 K results. (The larger cross section observed at 80 K is due to the participation of attractive terms in the interaction potential and is well-understood.[17]) Only a single peak was observed in the Gly_5Na^+ ATD, indicating the experimental data are clearly in line with the fully unfolded structure. This result demonstrates that a sodium coordination number of up to 5 is most favorable in these systems.

In summary, analysis of the cross section data conclusively indicates that for Gly_nNa^+, $n = 4-6$, these systems have charge solvation structures and no evidence for salt bridge formation is observed. These findings are consistent with ab initio and DFT calculations carried out on the smaller systems ($n = 1-4$) that favor charge solvation structures. This is most evident for Gly_2Na^+ where the salt bridge form is ~14 kcal/mol less stable than the charge solvation form (Table 1). While the MP2 and B3LYP geometry optimizations for Gly_2Na^+ lead to stable salt bridge structures corresponding to minima on the potential energy surfaces, this is not the case for Gly_3Na^+ and Gly_4Na^+. During geometry optimization of salt bridge structures an internal proton transfer from ($-NH_3^+\cdots{}^-OOC-$) to ($-NH_2\cdots$-HOOC−) takes place, while the rest of the peptide stays essentially in the same conformation. The energy gain for this proton transfer is ~5 kcal/mol. Values reported for Gly_3Na^+ and Gly_4Na^+ in Table 1 are strictly speaking energy differences between potential energy minima, one corresponding to an unfolded and the other to a compact charge solvation conformer. The energy of the real salt bridge structure is therefore ~5 kcal/mol higher than that of the compact charge solvation form, yielding a relative energy for the salt bridge of ~13 kcal/mol, a value close to the 13.7 kcal/mol for Gly_2Na^+ (Table 1). The DFT calculations are expected to give reliable results based on the near perfect agreement with the MP2 result obtained for $GlyNa^+$ at the highest level of theory (6-311++G**) as shown in Table 1. Furthermore, partial MP2/6-31G** optimizations of Gly_3Na^+ salt bridge structures are in qualitative agreement with the DFT result. Internal proton transfer is observed as well and connected with a ~6 kcal/mol energy gain. However, the resulting compact charge solvation conformation is relatively stable and only 0.5 kcal/mol less stable than the unfolded one. Details will be published elsewhere.[27]

For $GlyNa^+$ the situation regarding salt bridge formation is not quite as conclusive, but the charge solvation form is calculated to be 3 kcal/mol more stable at the level of theory utilized. Further evidence that $GlyNa^+$ does not form a salt bridge is supplied by additional cross section experiments carried out for glycine amide and glycine methyl ester. These two species cannot form a zwitterion because they lack the acidic hydrogen. Therefore their sodiated forms are expected to be charge solvation structures. As shown in Figure 6 it is found experimentally that the sodiated species have a 7−8% larger

(24) Note, that preliminary results reported (Wyttenbach, T.; Batka, J. J., Jr; Gidden, J.; Bushnell, J. E.; Bowers, M. T. *Proceedings 45th Conference Am. Soc. Mass Spectrom. Allied Topics*; Palm Springs, CA, 1997; p 368) are based on erroneous calculations of theoretical cross sections (see Appendix for correct treatment).

(25) There is a possibility that systematic errors could exist for the calculated cross sections of the sodiated glycines. These structures are quasi planar "open" structures while both the salt bridge and protonated structures are quasi spherical. We have observed previously that experimental cross sections of quasi spherical structures can be essentially exactly fit (ref 17) using a modified projection model (refs 10 and 17). However, for quasi planar species such as cesiated 18-crown-6 ether, we have noticed calculated cross sections are larger (by 3−5%) than experiment. Hence, the current version of the projection model may systematically overestimate the cross sections of "planar" species by a few percent while doing a better job with near spherical species. One possible solution is to calculate the collision integral numerically (ref 26). These are very time-consuming calculations, however, and hence the 100 calculations we do for each system to obtain a scatter plot are not feasible. This issue is under active investigation. At present normalizing the calculated cross section of sodiated diglycine to experiment and adjusting the remaining calculations accordingly (for $n = 3-6$) should yield a more accurate indication of the true model cross sections than the calculations themselves. At the very least it serves to show the trend in the experiments with size is very accurately reproduced by the charge solvation calculations but not by the salt bridge calculations.

(26) Shvartsburg, A. A.; Jarrold, M. F. *Chem. Phys. Lett.* **1996**, *261*, 86. Shvartsburg, A. A.; Schatz, G. C.; Jarrold, M. F. *J. Chem. Phys.* **1998**, *108*, 2416.

(27) Wyttenbach, T.; Bowers, M. T. Unpublished results.

cross section than the protonated species for all three cases, glycine, glycine amide, and glycine methyl ester. By using the lowest energy charge solvation structure from model calculations for the sodiated forms, the sodiated molecules have a 6−7% larger cross section than the protonated forms in good agreement with experiment. However, if we use the lowest energy salt bridge form for $GlyNa^+$, only a ∼4% increased cross section over $GlyH^+$ is predicted, a result in clear disagreement with experiment. If, in fact, the calculated ester (or amide) cross section differences are normalized to give agreement between the charge solvation structure and experiment, then essentially perfect agreement is obtained for the charge solvation structure for sodiated glycine itself. The clear conclusion is that $GlyNa^+$ has the charge solvation structure and not the salt bridge structure at thermal energies. It should be noted, however, that $(H_3N^+-CH_2-COO^-)Na^+$ has theoretically been located as a stable isomer (although not the *most* stable one) as opposed to the un-sodiated glycine zwitterion $H_3N^+-CH_2-COO^-$ which is not a stable structure and converts without barrier into the 15−20 kcal/mol more stable H_2N-CH_2-COOH form.[3] The addition of a sodium ion stabilizes the zwitterion considerably relative to the nonzwitterion form (by more than 10 kcal/mol) but not sufficiently to make the salt bridge the most stable form.

Conclusions

The combined ab initio/DFT, molecular mechanics, and ion mobility approach applied in this study to oligoglycines provides no evidence for the existence of salt bridge structures for the sodiated species. All the observations, from experiments and calculations, are in favor of charge solvation structures. Sodiated oligoglycines have systematically larger experimental cross sections than protonated oligoglycines, which is in line with the unfolded charge solvation Gly_nNa^+ and compact Gly_nH^+ structures found by molecular mechanics. Ab initio and DFT calculations also indicate that charge solvation forms are more stable for the sodiated species in all cases for $n = 1-4$.

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Appendix: Cross Section Calculations

Momentum-transfer collision integrals, the quantity determined in ion mobility experiments,[21] are approximated for model structures by orientation averaged projection cross sections, which are calculated by a Monte Carlo integration. For mostly convex bodies these two quantities have very similar values.[26] For a description of the projection approximation see ref 10; to determine atomic collision radii see ref 17. The following He-X Lennard-Jones parameters (position and depth of well) have been used for ions with 60 atoms and more: $r_{LJ(60)} = 2.38$ Å (X=H), 2.70 (Na), 3.02 (C, N, O), $\epsilon_{LJ(60)} = 0.34$ kcal/mol (H), 0.36 (Na), 0.37 (C, N, O). For ions with <60 atoms potential wells are shallower and the parameters were scaled by empirical formulas obtained from carbon cluster data:[27]

$$r_{LJ}(N_a)/r_{LJ(60)} = 1.06 - (1.95 \times 10^{-3})N_a + (1.67 \times 10^{-5})N_a^2$$

$$\epsilon_{LJ}(N_a)/\epsilon_{LJ(60)} = 9.8 \times 10^{-2} + (3.09 \times 10^{-2})N_a - (2.65 \times 10^{-4})N_a^2$$

with N_a being the number of atoms.

Supporting Information Available: (A) B3LYP Geometries for $GlyNa^+$ and Gly_nNa^+ ($n = 1-4$) and cartesian coordinates and energies for 2 $GlyNa^+$, 3 Gly_2Na^+, 4 Gly_3Na^+ and 2 Gly_4Na^+ isomers; (B) frequencies (B3LYP) for $GlyNa^+$ and Gly_2Na^+; (C) molecular mechanics geometries for Gly_5H^+ and Gly_5Na^+; cartesian coordinates of structures shown in Figure 4 (9 pages print/PDF). See any current masthead page for ordering information and Web access instructions.

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