Comprehensive Density Functional Theory Study on Serine and Related Ions in Gas Phase: Conformations, Gas Phase Basicities, and Acidities

Ren Miao, Chen Jin, Gaosheng Yang, Jin Hong, Chunmei Zhao, and Longgen Zhu*

State Key Laboratory of Coordination Chemistry, Coordination Chemistry Institute,Nanjing University, Nanjing 210093, P. R. China

Received: October 9, 2004; In Final Form: January 7, 2005

Density functional theory (DFT) calculations have been performed to investigate the gas-phase conformations of serine and its three related ions (serineH$^+$, serine$^-$, and serine^{2-}). The full ensemble of possible conformations, 324 conformations for serine, 108 for serineH$^+$, 162 for serine$^-$ and 54 for serine^{2-}, were first surveyed at B3LYP/6-31G* level, and then the obtained unique conformations were further refined at B3LYP/6-311+G** level. From full optimizations, 74 unique conformations for seine, 14 for serineH$^+$, 11 for serine$^-$, and 4 for serine^{2-} were located, and their relative energies were also determined at B3LYP/6-311+G** level. Atoms in molecules (AIM) analysis was carried out to establish rigorous definition of hydrogen bonds. Six types of intramolecular H-bonds in conformers of serine, six types in serineH$^+$, three types in serine$^-$, and two types in serine^{2-} were identified within the framework of AIM theory and their relative strengths were determined based on topological properties at bond critical points (BCPs) of H-bonds. The intramolecular H-bonds were demonstrated to play an important role in deciding the relative stability of conformations of amino acids and the related ions. The enthalpies and Gibbs free energies of protonation and deprotonation reactions of serine and its related ions were calculated at B3LYP/6-311+G**//B3LYP/6-31G*, and B3LYP/6-311+G**//B3LYP/6-311+G** level. The calculated results are both in excellent agreement with the experimental data. We demonstrate in this study that B3LYP is an efficient and accurate method to predict the thermochemical and structural parameters of amino acids and the related ions.

1. Introduction

A considerable interest of computational chemists has been focused on amino acids,[1−15] which have tremendous chemical, biochemical and biological significance. Owing to a variety of intramolecular interactions and extreme conformational flexibility, studies of their potential energy surface (PES) is not readily amenable to experiments, which is hindered further by the low volatility of amino acids and their ready thermal decomposition. Nevertheless, the tractable size of most amino acids makes it possible that high-level ab initio electronic structure calculations can provide experimentalists with numerous valuable data to help guide them in efforts to identify gaseous amino acids by the microwave spectra.

Among the 20 amino acids, the conformational complexity differs notably. As the structurally simplest amino acids, glycine and alanine are the most widely studied ones. In the past decades, several groups have carried out studies of glycine and alanine using methods including the electron correlation.[16−22] According to their results, the intramolecular hydrogen bonds (H-bonds) formed between the amino group and carbonyl oxygen ($NH_2\cdots O{=}C$) is always observed.

However, as the size of amino acid becomes larger, conformation complexity increases significantly. More single-bond rotamers and intramolecular H-bonds existing in these molecules lead to the stable conformations severalfold more than those of glycine and alanine. For instance, serine has a hydrogen-bonding group, CH_2OH, which leads to a level of complexity not found in simple amino acids such as glycine or alanine. The added molecular size and possibility of having CH_2OH to serve as H-bond donor or acceptor make the conformational study of serine a challenging task. In the recent years, some conformational investigations of serine at relatively high-level theory have been reported.[23−25] The 324 possible conformations (trial structures) of serine were proposed by Gronert et al., first optimized at semiempirical AM1 level and then the obtained unique conformers were further refined at the HF/6-31G* level, the stabilizing contributions of various H-bonds were also qualitatively analyzed.[23] However, as they stated in their work,[23] despite their comprehensive choice of the initial trial structures, the inadequacy of initial semiempirical AM1 optimization may unavoidably cause missing of some stable conformers. The lowest conformers of serine and its protonated species in gas phase were also located by substituting hydrogen atom in the most stable conformation of well-studied glycine by CH_2OH group, and the proton affinity of serine in gas phase was calculated.[24] This original study also shed light on the possible conformational connection between serine and its protonated species in gas phase. Nevertheless, the conformation-searching approach used in the study[24] is suffering from its intrinsic deficiency: it merely scans a subset of possible conformations, and is very likely to exclude some stable conformations. Therefore, it is necessary to consider the full ensemble of possible conformations and to use high-level theoretical method throughout in conformation-searching procedure in order to obtain the comprehensive and accurate characterization of conformations of serine and its related ions in gas phase.

Accurate location of the lowest conformations of neutral amino acid and the related ions are prerequisites for precise

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* Corresponding author. E-mail address: Zhulg@public1.ptt.js.cn.

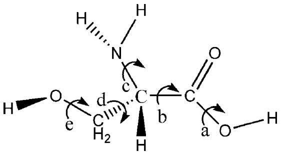
10.1021/jp0453919 CCC: $30.25 © 2005 American Chemical Society
Published on Web 02/22/2005

computations of gas-phase thermochemical parameters, such as gas-phase basicities and proton affinities, which are of fundamental significance in understanding the chemistry of amino acids or peptides. Numerous experimental studies have been done to measure these biologically important properties.[26−30] However, theoretical studies are scarcely reported and mainly focus on the simplest amino acids, e.g., glycine and alanine.[31−34] Conformations of neutral and protonated serine and its proton affinity and intrinsic basicity in gas phase have been studied by Noguera et al.;[24] however, as stated above, the conformation-searching approach has an intrinsic deficiency. Therefore, by comprehensive and accurate location of the lowest conformations of serine and its related ions, it is expected that one can obtain more reliable values of gas-phase proton affinity and basicities. Besides protonation, deprotonation is as well an important property of amino acids, which can be frequently observed in biological activities. Gas-phase acidities of some α-amino acids have previously been measured in the gas phase by kinetic method activated by collision.[35] To the best of our knowledge, there seems so far no theoretical calculation dealing with the proton dissociation energies and gas-phase acidity of serine. We perform a theoretical study of the gas-phase acidity of serine and serine$^-$ in this study, and this will also serve as a good test of accuracy of the approach used in this study (initial optimization at B3LYP/6-31G* and then refined at B3LYP/6-311+G**).

Intramolecular H-bond in amino acids has long been recognized and considered to be a weighty factor in relative stability of conformers of amino acids.[23] Nevertheless, there is no general agreement as to which factors consist of the necessary criteria to conclude the existence of an H-bond. In the previous studies, geometric criteria have been frequently used; e.g., a distance of 2.75 Å has been taken as a cutoff for near-atom interactions.[23] The geometric criteria are always considered to be too simplistic, and to some extent, arbitrary. In some of the latest studies, Bader's atoms in molecules (AIM) theory[36] has been used to characterize intramolecular hydrogen bonds existing in glycine,[37] proline,[38] and Vigabatrin amino acid.[39] AIM theory essentially deals with the molecular electron density and was first used to describe intermolecular H-bonds, and it was later found to be also applicable in characterization of intramolecular H-bonds.[40] Within the framework of the AIM theory, hydrogen bonding may be defined by several consecutive AIM-based criteria.[37] Moreover, topological parameters at bond critical points (BCPs) of H-bonds (e.g., electron density ρ_b) have been found able to provide invaluable information in terms of geometric properties and the relative strengths of H-bonds. Thereby, AIM analysis is further performed in this study, with an intention to obtain a rigorous definition and insightful understanding of intramolecular H-bonds existing in serine and its related ions.

The objective of the present study is 2-fold. One objective is to determine all the stable conformations of serine and the related ions (protonated serineH$^+$, deprotonated serine$^-$ and serine^{2-}) and to establish a rigorous definition of intramolecular H-bonds existing in their conformers within the framework of AIM theory. The influence of H-bonds upon the relative stability of conformations is further analyzed. The second objective is to calculate the theoretical values of intrinsic basicities/acidities and proton affinities/proton dissociation energies of serine and its related ions and then to compare them with experimental data to examine the accuracy of the approach employed in this study.

SCHEME 1



a 2-fold: 0, 180 (except serine$^-$ and serine^{2-})
b 6-fold: 30, 90, 150, 210, 270, 330
c 3-fold: -60, 60, 180 (except serine$^+$)
d 3-fold: 60, 180, 300
e 3-fold: 60, 180, 300 (except serine^{2-})

2. Method

As discussed above, amino acids can exist in a number of conformations owing to many single-bond rotamers present in the amino acids. In the previous studies of serine, two strategies were used to approach to stable conformations. The first approach, proposed by Gronert et al.,[23] chooses the set of trial structures by allowing for all possible combinations of single-bond rotamers. This approach has the advantage of considering the full ensemble of possible conformations; while the problem is the possible exclusion of some stable conformations in the initial optimization procedure, which has been normally done in the previous studies at low-level calculations in consideration for the computational cost, e.g., the semiempirical method (AM1) in the work done by Gronert et al.[23] The other approach is to derive the energy minima of serine from the lowest conformation of glycine by substituting one H of CH_3 with a CH_2OH group.[24] The intrinsic inadequacy of this approach is that it merely considers a subset of the possible conformations and is very likely to exclude some stable conformations.

In the present study, we adopt the first approach in order to obtain comprehensive and accurate description of conformations of serine and its related ions. All trial structures are considered, that is 324 structures for serine, 108 for serineH$^+$, 162 for serine$^-$, and 54 for serine^{2-}, as shown in Scheme 1. It has been pointed out that electron correlation must be included in any calculation involving amino acids in order to obtain reliable result.[37] Nguyen et al. have previously demonstrated that DFT methods could provide reliable structural and energetic characterization of conformers of amino acids, which is in good agreement with those obtained by MP2.[41] And B3LYP has recently proved to be able to recover the most important structural and energetic feature of amino acids.[38] Thus, we feel that B3LYP is a good choice of method for this study, considering its relative low computational cost compared to other traditional correlated method (MP2, MP4, etc.) and good accuracy. Gronert et al. have shown that geometries optimized using basis set 6-31G*, without diffuse functions, is able to provide reliable relative energies of conformations of amino acids.[23] Therefore, B3LYP/6-31G* is expected to be a reliable method for the initial geometry survey, and the exclusion of conformations resulting from inadequacy of low-level calculation is believed to be minimized. Each possible conformations (trial structures, totally 324 structures for serine, 108 for serineH$^+$, 162 for serine$^-$, and 54 for serine^{2-}) was first fully optimized at B3LYP/6-31G* level. Optimizations starting from different trial structures may lead to the same final structure; two structures are considered identical if their energy differences are less than 10^{-5} hartree, and the difference in dihedral angles is less than ca. 0.2°. Since it has been recently suggested that large basis sets with diffuse functions and polarization functions are needed to provide accurate structural and energetic characterization of H-bonds complexes,[42,43] the unique conformers obtained at B3LYP/6-31G* level were then subjected to full optimization at B3LYP/6-311+G** level, and again the unique structures were identified based on the criteria defined above. The obtained structures were confirmed to be true minima on PES by frequency analysis.

AIM electron density analysis was performed using B3LYP/6-311+G**//B3LYP/6-311+G** wave function.[44] For comparison, AIM analysis was also performed using B3LYP/6-311+G**//B3LYP/6-31G* wave function (results are listed in Tables S1−S4 in Supporting Information). Molecular dipole moments were calculated at B3LYP/6-311+G**//B3LYP/6-311+G** level.

The enthalpy and Gibbs free energy of each species were calculated using the B3LYP/6-311+G** electronic energy; zero-point vibrational energy, thermal corrections (0−298 K) and the entropy term was obtained at the same level (unscaled). It should be noted that all of the gas-phase thermodynamic parameters reported in this paper correspond to the reference state of 1 atm, 298 K.

All calculations were performed using Gaussian 98 program package[46] on SGI3800 workstation and Dawning workstation in Supercomputer Centre at Nanjing University.

3. Results and Discussion

3.1. Serine. From optimizations of full ensemble of possible conformations (324 trial structures), 83 unique conformations were identified at B3LYP/6-31G* level. Further refinement at B3LYP/6-311+G** level led to 74 unique stable conformers. Their nature of energy-minima was confirmed by without any imaginary frequency. The energies of obtained 74 conformations vary by ca. 14 kcal/mol. The relative energies calculated at B3LYP/6-311+G**//B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-311+G** are both listed in Table 1.

The relative energies predicted by B3LYP/6-311+G**//B3LYP/6-31G* are in good agreement with those predicted by B3LYP/6-311+G**//B3LYP/6-311+G**, the difference in relative energies is generally smaller than ca. 0.2 kcal/mol. This is consistent with the result of Gronert et al.,[23] which points out that the overall accuracy of MP2/6-31+G*//HF/6-31G* and MP2/6-31+G*//MP2/6-31+G* is almost indistinguishable when used in calculation of relative energies of amino acids. However, as listed in Table S1 (see Supporting Information), the relative energies predicted at B3LYP/6-31G*//B3LYP/6-31G* level are notably different from those predicted at high-level methods. This result suggests that as far as relative energies are concerned, results with acceptable accuracy can be obtained by performing single-point energy calculations at theoretical method including electron correlation and large basis set with diffuse functions, using the geometries optimized at relatively low level, in which diffuse functions (or even electron correlation) may not necessarily be included. This result is encouraging since B3LYP/6-31G* (or even HF/6-31G*) level is more tractable for larger systems, such as polypeptides and large amino acid derivatives.

Calculated rotational and total dipole moments for all conformers are also listed in Table 1 with a view to aiding future microwave and/or millimeter-wave spectroscopic studies of free serine. From the relative energies of serine conformers, it is expected that the equilibrium mixture should contain significant contributions from several conformers, while **1**, **2**, **3**, and **4** (conformer numbers in bold form here and in this section correspond to the column head no. listed in Table 1) play the most dominant roles. Microwave spectroscopy should be able to distinguish between these conformers due to their different rotational constants and dipole moments. Unfortunately, no experimental data are available for comparison with the theoretical values.

In the work done by Gronert et al.,[23] their systematic survey resulted in 51 unique conformations, which is 23 less than our results. Considering the high-level calculations used in the conformer-searching approach, 74 unique conformation identified in this study are believed to be the most comprehensive and accurate description of serine conformers to date. The lowest 8 conformations located by Gronert et al. at MP2/6-31+G*//HF/6-31G* level correspond to **2**, **1**, **4**, **6**, **3**, **12**, **13**, and **16** in this study, which are in general agreement with our results. Noguera located 8 conformations (Ser 1−Ser 8) by substituting H atom of CH_3 with CH_2OH group,[24] which correspond to **1**, **3**, **2**, **8**, **10**, **18**, **21**, and **24** in the present study. The lowest conformations **1**, **2**, and **3** are successfully identified, which indicates this approach can be used to locate the lowest conformations of amino acids. However, no comprehensive conclusion can be drawn owing to exclusion of a large part of stable conformations.

Electron density analysis within framework of AIM theory was performed in order to obtain rigorous definition and insightful understanding of intramolecular H-bonds existing in serine conformers. We followed the proposal of Sadlej-Sosnowska et al.,[39] where several consecutive criteria were used to conclude the existence of hydrogen bond: (a) The H-bond donor−acceptor distance was smaller than ca. 3 Å; this criterion ensures mutual penetration of the hydrogen and acceptor atom van der Waals envelopes. (b) One bond critical point (BCP) was determined on the bond path linking H-bond hydrogen and acceptor atom, characterized by a relatively small density electron (ρ_b) and positive Laplacian ($\nabla^2\rho$). The existence of BCP linking hydrogen and acceptor is considered to be a crucial criterion.[47] (c) The charge on the H-bond hydrogen decreases in comparison with that on the non-H-bond hydrogen; i.e., loss of charge on the hydrogen atom occurs in the formation of H-bond. These three criteria have been successfully used by Sadlej-Sosnowska et al. to characterize intramolecular H-bond existing in a large number of conformers of Vigabatrin amino acid.[39]

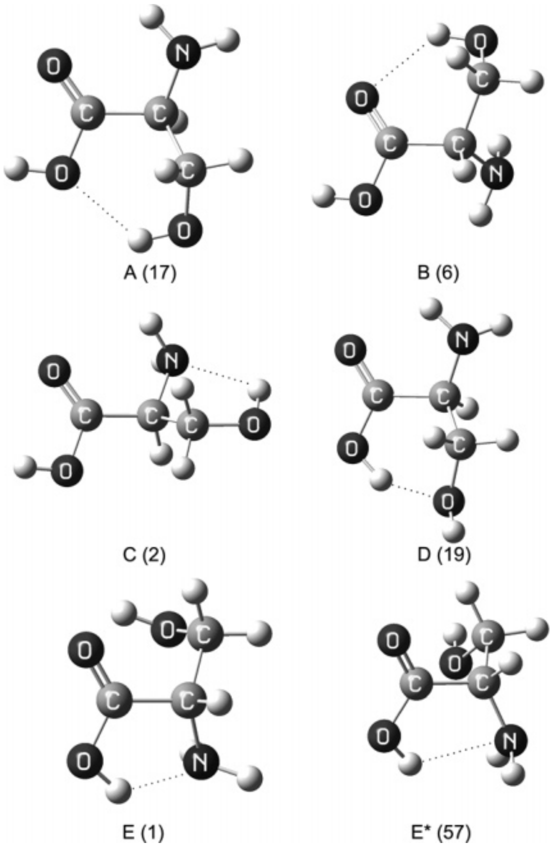
As listed in Table 1, we found five types of H-bond existing in all serine conformers: type A is $CH_2OH\cdots O(H)\text{-}C{=}O$, type B is $CH_2OH\cdots O{=}C{-}OH$, type C is $CH_2OH\cdots NH_2$, type D is $O{=}C{-}OH\cdots OH{-}CH_2$, and type E is $O{=}C{-}OH\cdots NH_2$. As an H-bond donor, hydroxyl group interacts with carboxyl OH, carbonyl O, and NH_2 groups. Carboxyl OH also serves as an H-bond donor to interact with hydroxyl OH and NH_2. However, within the framework of AIM theory, no hydrogen bond was found between H of NH_2 group and other acceptors (no BCP was found). The same behavior has been observed in ref 37. This may be understood by the conventional chemical concept that NH_2 group is a weak hydrogen bond donor, and the steric constraints imposed by the backbone of amino acid molecule prevent the formation of an H-bond with NH_2 group as donor (five-membered ring has to be formed in order to form an H-bond with NH_2 as donor). As a potential hydrogen bond acceptor widely present in many macromolecules and biomolecules such as DNA and protein, the amino group has been proposed to be able to accept hydrogen bonds and may play a mechanistic role in catalytic processes such as deamination or amino transfer.[48] In total, there are 6 A-type, 8 B-type, 6 C-type, 7 D-type, and 11 E-type H-bonds found in 74 unique conformers (see Figure 1 for a sample conformer of each bond type).

As for type E H-bonds, two different bonding schemes were found. One scheme is in accordance with traditional image of hydrogen bond (see E (**1**) in Figure 1), H-bond hydrogen interacts with the lone pair of nitrogen; while the other (labeled with E*) seems to interact with nitrogen from the opposite side (see E*(**57**) in Figure 1).

TABLE 1: Calculated Relative Energies, Interaction Distances, Selected Topological Properties at BCPs, Rotational Constants, and Dipole Moments for Conformers of Neutral Serine

	relative energy[a]							rotational constants[f]			
no.	6-31G*	6-311+G**	n[b]	bond[c]	distance[d]	ρ_b[e]	$\nabla^2\rho_b$[e]	A	B	C	dipole[g]
1	0.00	0.00	1	E	1.918	0.0357	0.1051	3.5582	2.3148	1.7098	4.24
2	−0.14	0.02	1	C	2.245	0.0193	0.0715	4.4833	1.8057	1.4344	2.10
3	0.18	0.36	2	B	2.051	0.0222	0.0770	3.6261	2.3687	1.5077	5.15
				E	1.937	0.0343	0.1032				
4	0.74	0.89	1	C	2.278	0.0184	0.0704	3.5703	2.2410	1.7569	3.02
5	1.27	1.51	1	E	1.913	0.0359	0.1053	4.5268	1.8317	1.4512	4.70
6	1.46	1.56	1	B	2.190	0.0170	0.0594	3.9673	2.1855	1.6539	2.75
7	1.37	1.57	1	E	1.929	0.0348	0.1035	4.4788	1.8140	1.4469	4.53
8	1.48	1.59	1	C	2.251	0.0191	0.0711	4.5215	1.7587	1.4626	3.44
9	1.53	1.72	1	E	1.921	0.0353	0.1052	4.6099	1.8444	1.3760	4.63
10	2.24	2.22	1	B	2.219	0.0161	0.0571	3.5035	2.3102	1.5600	3.17
11	2.38	2.46	1	E	1.911	0.0361	0.1059	4.5441	1.8266	1.3693	4.28
12	2.28	2.46	0					3.4859	2.2506	1.7667	2.64
13	2.53	2.60	0					3.4678	2.3171	1.7012	2.65
14	2.44	2.61	1	B	2.176	0.0175	0.0612	3.6608	2.3191	1.5043	3.04
15	2.69	2.76	1	B	2.146	0.0185	0.0639	3.9807	2.1193	1.6869	2.27
16	2.59	2.76	1	C	2.256	0.0190	0.0710	3.6172	2.2072	1.7542	3.80
17	2.67	2.89	1	A	2.155	0.0170	0.0654	3.5266	2.3779	1.4932	1.25
18	2.73	2.91	1	A	2.130	0.0180	0.0675	3.3345	2.4312	1.5208	1.82
19	2.95	3.12	1	D	1.805	0.0359	0.1240	3.4821	2.4775	1.5278	4.95
20	3.04	3.22	1	A	2.143	0.0176	0.0673	3.9034	2.1052	1.7199	1.63
21	3.08	3.30	0					3.5309	2.2178	1.7743	0.59
22	3.25	3.31	0					3.5892	2.1015	1.7609	2.80
23	3.19	3.33	1	E	1.936	0.0343	0.1038	4.5335	1.8288	1.3629	5.43
24	3.27	3.42	0					4.4227	1.7883	1.4461	2.66
25	3.34	3.54	0					4.4506	1.7954	1.4557	3.22
26	3.51	3.61	0					2.9845	2.4518	1.6998	2.47
27	3.46	3.68	0					4.8451	1.7928	1.3800	0.82
28	3.47	3.68	0					4.6365	1.8473	1.3772	2.27
29	3.65	3.74	1	D	1.818	0.0365	0.1159	3.9039	2.2420	1.7312	4.78
30	3.63	3.80	0					3.0470	2.3513	1.7441	0.37
31	3.76	3.85	1	D	1.806	0.0363	0.1215	3.4964	2.4520	1.5185	5.48
32	3.71	3.90	1	A	2.180	0.0163	0.0593	3.3022	2.4450	1.5577	0.87
33	3.93	3.97	1	D	1.812	0.0359	0.1211	3.4144	2.4617	1.5127	4.51
34	3.87	4.00	1	B	2.098	0.0198	0.0691	3.4901	2.3906	1.5271	2.61
35	4.01	4.09	0					3.3701	2.2309	1.8381	1.75
36	4.12	4.23	1	A	2.207	0.0156	0.0572	3.7897	2.0608	1.8016	1.06
37	4.08	4.24	0					3.0298	2.3456	1.7569	1.64
38	4.18	4.31	0					4.3690	1.7786	1.4575	1.17
39	4.21	4.40	0					4.5932	1.8295	1.3698	3.14
40	4.27	4.45	0					4.8165	1.7772	1.3682	2.83
41	4.33	4.48						4.4477	1.7469	1.4725	1.08
42	4.37	4.58	0					3.1166	2.2916	1.7684	2.85
43	4.40	4.60	0					4.4900	1.7496	1.4843	3.33
44	4.45	4.60	1	D	1.825	0.0338	0.1209	3.8197	2.1882	1.7379	5.13
45	4.54	4.69	1	E	2.021	0.0280	0.0940	3.4461	2.1838	1.8839	6.32
46	4.63	4.80	0					3.0279	2.4209	1.6920	2.36
47	4.65	4.85	0					3.3913	2.2420	1.8397	3.87
48	4.80	5.00	0					3.0902	2.3020	1.7376	2.36
49	4.98	5.17	0					3.4358	2.2175	1.8439	2.60
50	5.15	5.28	0					4.4189	1.7318	1.4876	3.10
51	5.32	5.45	0					3.4043	2.1684	1.8515	2.73
52	5.41	5.56	0					3.0425	2.3574	1.7373	2.57
53	5.55	5.70	1	C	2.262	0.0188	0.0715	4.4367	1.7990	1.4363	2.22
54	5.64	5.80	1	A	2.419	0.0112	0.0415	3.4196	2.4232	1.6751	3.10
55	5.91	6.11	0					3.1013	2.2970	1.7568	4.30
56	6.69	6.82	0					3.5817	2.2756	1.7081	4.52
57	6.85	6.99	1	E*	2.257	0.0191	0.0708	3.5175	2.1591	1.8444	4.09
58	7.09	7.23	0					3.1342	2.2501	1.7456	2.52
59	7.17	7.39	0					3.5517	2.1122	1.5724	4.06
60	7.30	7.43	1	E*	2.231	0.0199	0.0710	4.5540	1.8224	1.3722	4.99
61	7.37	7.46	1	D	1.885	0.0300	0.1080	3.7792	2.1512	1.7814	6.97
62	7.55	7.66	1	B	2.122	0.0194	0.0677	3.9977	2.1254	1.6758	3.60
63	7.90	8.09	1	E	1.962	0.0325	0.1024	3.7205	2.1548	1.4536	6.55
64	8.30	8.35	1	B	2.407	0.0117	0.0446	3.3111	2.2814	1.6559	3.44
65	8.61	8.53	1	D	1.867	0.0317	0.1094	3.7584	2.1528	1.7620	6.65
66	8.81	8.98	0					3.4739	2.2553	1.7358	4.97
67	8.80	8.98	0					4.4019	1.7510	1.4873	4.24
68	8.95	9.13	1	C	2.256	0.0188	0.0715	4.6590	1.6498	1.4974	2.89
69	9.44	9.59	0					4.3990	1.7519	1.4702	4.45
70	9.73	9.95	0					4.5403	1.8380	1.3835	4.19
71	10.39	10.47	0					3.3543	2.2245	1.8394	4.41
72	11.10	11.30	0					4.5633	1.8178	1.3669	4.67
73	11.84	11.95	0					3.1217	2.2248	1.7234	3.59
74	14.02	14.20	0					3.1247	2.2502	1.7439	7.13

[a] 6-31G* and 6-311+G** denote relative energies calculated at B3LYP/6-311+G**//B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-311+G**, respectively (in kcal/mol). [b] *n* denotes number of hydrogen bonds identified in the conformer. [c] Six types of H-bond were found in serine conformers, A denotes $CH_2OH\cdots O(H)\text{-}C{=}O$, B denotes $CH_2OH\cdots O{=}C{-}OH$, C denotes $CH_2OH\cdots NH_2$, D denotes $O{=}C{-}OH\cdots OH{-}CH_2$, E denotes $O{=}C{-}OH\cdots NH_2$, E* denotes another type E bonding (see below for details). [d] Interaction distance between H-bond hydrogen atom and H-bond acceptor atom (in Å). [e] Electron density and its Laplacian calculated at BCPs, in atomic units. [f] In GHZ. [g] In Debye.


A (17) B (6)

C (2) D (19)

E (1) E* (57)

Figure 1. Sample conformers optimized at B3LYP/6-311+G** level. Each represents one type of H-bond, which is illustrated with dashed line. Number in parentheses (corresponding to the column head no. in Table 1) indicates the conformer in which hydrogen bond exists.

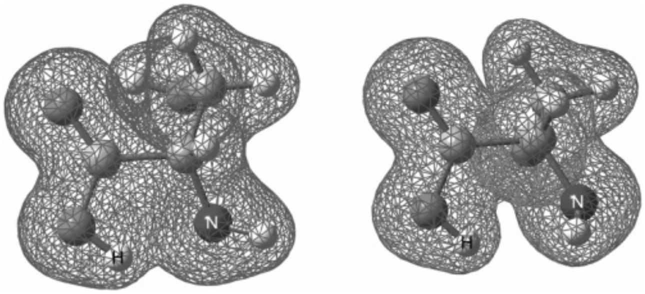


Figure 2. Illustrations of molecular electron density distribution (contour value = 0.025 au) of conformers containing type E H-bond (conformer **1**) (left) and E* (conformer **57**) (right). H and N labeled indicate the H-bond hydrogen and the acceptor atom.

The difference can be more intuitively understood by their different molecular electron density distribution patterns (see Figure 2). The notable discrepancy in the vicinity of hydrogen bond is the larger electron density between H-bond H and N in type E and the larger density on N of type E* on the opposite side to H-bond. This indicates that the lone pair of nitrogen in type E* bond mainly resides at the side opposite to H-bond and is likely to make less a contribution to the formation of H-bond than type E.

The average geometric and topological parameters of six bond types are gathered in Table 2. From data listed in Tables 1 and 2, it is apparent that all these six bond types satisfy criteria for hydrogen bond, which are (a) existence of BCP, (b) relatively small electron density value and positive Laplacian at BCP, and (c) loss of electron density on H-bond hydrogen.

TABLE 2: List of Average Geometric and Topological Properties of Six Bond Types (A, B, C, D, E, E*)

	bond type					
property	A	B	C	D	E	E*
n^a	6	8	6	7	9	2
dist (Å)	2.206	2.176	2.258	1.831	1.939	2.244
std dev	0.108	0.107	0.011	0.032	0.035	
$\rho_b{}^b$	0.0159	0.0178	0.0189	0.0343	0.0341	0.0195
std dev	0.0025	0.0031	0.0003	0.0026	0.0025	
$\rho_H{}^b$	0.4267	0.4225	0.4208	0.4024	0.4008	0.4211
ref value^c	0.4312	0.4312	0.4312	0.4263	0.4263	0.4263
$\Delta\rho_H$	−0.0045	−0.0087	−0.0104	−0.0239	−0.0255	−0.0052

[a] Total number of hydrogen bonds of each type existing in all 74 unique conformers; [b] In atomic units; [c] Reference values were obtained by averaging electron densities of corresponding hydrogen in conformers **69**−**74** (six conformers were taken into account in order to minimize possible error), in which no hydrogen bond was found.

Types E and E* also differ notably in terms of the geometric and topological parameters. The average interaction distance for E is much shorter than E* (1.939 and 2.244 Å for E and E*, respectively); consequently, ρ_b of H-bond for E is considerably larger. The H−N−H angles of amino group show different values as well. The average angle is 107.4° for type E, while the value increases to 113.6° in the case of type E*. For comparison, the average angle of 109.8° was obtained for conformer **69**−**74**, in which no hydrogen bond was found. The lone pair of nitrogen directly interacts with H-bond hydrogen in E, thus decrease in H−N−H angles can facilitate the formation of a type E H-bond. Nevertheless, in the case of E*, the majority of lone pair resides at the side opposite to the H-bond (see Figure 2 for illustration of molecular electron density distribution), and an increase in H−N−H angles, i.e., tending to form a planar structure, should favor the formation of an E* type H-bond.

Examining the interaction distances ($r_{H\cdots X}$) and ρ_b of H-bonds listed in Table 1, we noticed that for the same type of H-bonds, values of $r_{H\cdots X}$ and ρ_b may vary to a considerable extent (especially for type A and B H-bonds), and calculated standard deviations are listed in Table 2. For instance, type A H-bonds vary in interaction distance from 2.130 to 2.419 Å; therefore, values of ρ_b also exhibit noticeable variation. It has been found that there are good correlation relationship between magnitudes of ρ_b and H-bond energies.[39,47] Due to the complexity of serine conformations, interaction distances and ρ_b of intramolecular H-bonds are conformer-dependent, as even H-bonds of the same type may show considerable variation. On the basis of the average values listed in Table 2, we are still able to estimate the average relative strengths of the six types of H-bonds, which gives D > E > E* > C > B > A. It has been recently reported that the ρ_b of H-bond also correlates with $r_{H\cdots X}$ (H···X indicates intramolecular hydrogen bond).[49] Our results also support this proposal: obtained linear correlation coefficient amounts to 0.95.

Some trends in terms of relationship between intramolecular H-bonds and relative stability of conformation could be observed statistically. Among the lowest 10 conformers (conformer **1**−**10**), each has one or two (conformer **3** contains two H-bonds) H-bonds, with, in total, three B, three C, and five E H-bonds (B, C, E are all considered to be relatively strong H-bonds). Contrarily, among the highest six conformers (conformer **69**−**74**), none of them contains an H-bond. This indicates that existence of the H-bond should be considered to be an important factor in the relative stability of conformers of amino acids.

It must be mentioned here that the relative stability of conformers of amino acids is a multidimensional function, which is decided by a number of factors. Intramolecular H-bond is merely one of the important factors. For instance, it has been pointed out that the energy of the *Z* (cis) COOH arrangement is about 5 kcal/mol lower than that of the *E* (trans).[38] However, no H-bond was found between carbonyl O and carboxyl OH in the *Z* (cis) arrangement; therefore, its increased stability could not be explained by H-bonds.

In the relative energies subsection, we demonstrated that B3LYP/6-311+G**//B3LYP/6-31G* level calculation are able to provide relative energies similar to those predicted at B3LYP/6-311+G**// B3LYP/6-311+G**, as listed in Table 1. Since the basis set 6-31G* would be more tractable for large systems, we further extended our study to investigate the accuracy at B3LYP/6-311+G**//B3LYP/6-31G* level when used in identifying the intramolecular H-bonds. By comparing geometries optimized at these two levels, we found that they generally provide very similar geometric parameters for the covalence bonds, e.g. the difference in bond lengths is usually smaller than 0.02 Å. It is observed that the interaction distances ($r_{H\cdots X}$) of H-bonds may exhibit larger variation than covalence bonds, as listed in Table 1 and Table S1. For instance, the average difference in interaction distances for the lowest 10 conformers (conformers **1**−**10**) amounts to ca. 0.07 Å. Although the difference is discernible, the intramolecular bonding scheme (H-bond type) predicted by B3LYP/6-311+G**//B3LYP/6-31G* are generally in accordance with that predicted by B3LYP/6-311+G**, especially for the lowest conformers, which play the most important role in conformer study. Values of ρ_b at BCPs of H-bonds predicted by B3LYP/6-311+G**//B3LYP/6-31G* are also moderately different from those predicted by B3LYP/6-311+G**//B3LYP/6-311+G**; however, the relative magnitude of ρ_b, i.e., the relative strength of H-bonds, determined at two levels are generally in agreement. This is consistent with the conclusion of Gronert et al., which states that it is the intramolecular nature of the interaction that severely limits the basis set superposition error normally encountered in hydrogen-bonding situations and makes the amino acids insensitive to changes in the basis set.[23] The results indicates that basis set 6-31G* could be used to recover the most important structural, energetic and intramolecular bonding features. Because of its relative low computational cost, tractable size of the basis set, and included electron correlation, B3LYP/6-31G* appears to be an attractive method for calculation of large amino acids, peptides, or their derivatives.

It is also noticed that in a few conformers the difference in interaction distances may be larger than the average values and result in modification of intramolcular bonding scheme (H-bonds). For instance, conformer **60** (corresponding to conformer **67** in Table S1) was determined to contain one H-bond (type E*) at B3LYP/6-311+G**//B3LYP/6-311+G** level; two H-bonds (type C and E*) were identified at B3LYP/6-311+G**//B3LYP/6-31G*. Nevertheless, the modification mostly occurs in the high-energy conformers and is expected to have little effect on the overall conclusion.

3.2. SerineH$^+$. The possible protonation sites in serine include the nitrogen of the amino group and the oxygen of the carbonyl group. It has been pointed out that the preferred site is the nitrogen atom, and the protonation on carbonyl oxygen is highly energetically unfavorable.[24] Therefore, we did not discuss the proton affinities of carbonyl oxygen in the present study.

Optimizations of the full ensemble of possible conformation (108 trial structures, since rotor **c** disappears upon protonation) led to 21 conformations, and further optimization at B3LYP/6-311+G** level gave 14 unique conformations, which were confirmed to be true energy minima on PES of serineH$^+$, judged by without any imaginary frequency. The energies of obtained 14 unique conformations vary by ca. 14 kcal/mol. The relative energies calculated at B3LYP/6-311+G**//B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-311+G** are both listed in Table 3. Again, these two methods predict very similar relative energies for conformers of serineH$^+$.

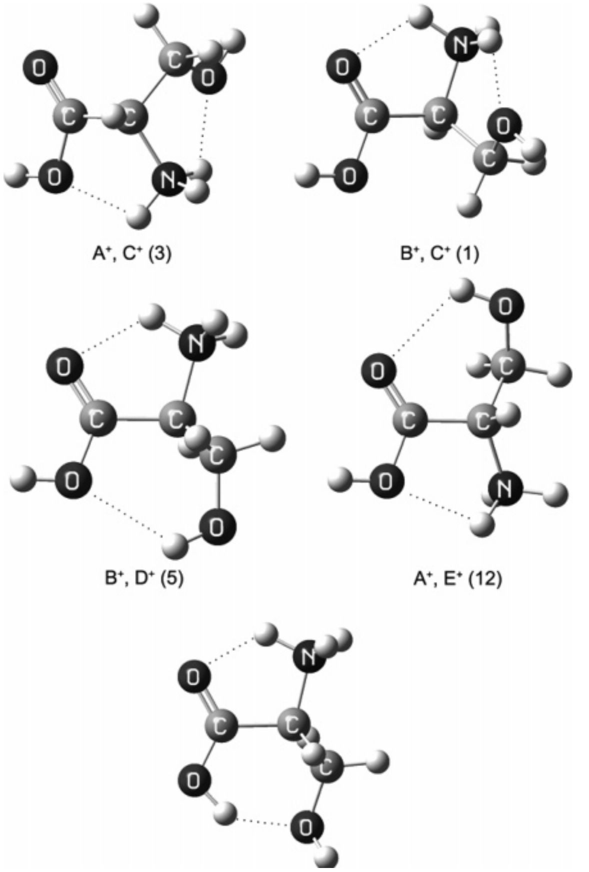
TABLE 3: Calculated Relative Energies, Interaction Distances, and Selected Topological Properties at BCPs for Conformers of Protonated Serine (serineH$^+$)

	relative energy[a]						
no.	6-31G*	6-311+G**	n[b]	bond[c]	distance[d]	ρ_b[e]	$\nabla^2\rho_b$[e]
1	0.00	0.00	2	B^+	1.994	0.0273	0.1107
				C^+	2.000	0.0250	0.1060
2	0.41	0.41	2	B^+	2.128	0.0216	0.0980
				C^+	1.987	0.0257	0.1094
3	3.21	3.19	2	C^+	1.986	0.0255	0.1104
				A^+	2.103	0.0205	0.0976
4	3.78	3.77	1	C^+	2.003	0.0248	0.1074
5	9.13	9.14	2	B^+	1.964	0.0290	0.1144
				D^+	2.480	0.0099	0.0380
6	9.55	9.60	1	B^+	1.988	0.0278	0.1105
7	9.70	9.70	1	B^+	1.906	0.0327	0.1235
8	9.73	9.74	2	B^+	2.038	0.0255	0.1058
				C^+	2.008	0.0249	0.1060
9	10.07	10.06	2	B^+	1.796	0.0418	0.1368
				F^+	1.850	0.0323	0.1137
10	10.16	10.17	2	B^+	1.892	0.0338	0.1273
				C^+	2.031	0.0237	0.1011
11	10.31	10.33	1	B^+	1.976	0.0283	0.1116
12	12.01	11.97	2	E^+	2.403	0.0117	0.0415
				A^+	2.180	0.0185	0.0939
13	13.88	13.92	0				
14	14.34	14.36	0				

[a] 6-31G* and 6-311+G** denote relative energies calculated at B3LYP/6-311+G**//B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-311+G** level, respectively (in kcal/mol). [b] *n* denotes number of H-bonds found in the conformer. [c] Six types of H-bond were found in serineH$^+$ conformers: A^+ denotes $NH_3\cdots O(H)\text{-}C{=}O$, B^+ denotes $NH_3\cdots O{=}C{-}OH$, C^+ denotes $NH_3\cdots OH{-}CH_2$, D^+ denotes $CH_2OH\cdots\text{-}O(H)\text{-}C{=}O$, E^+ denotes $CH_2OH\cdots O{=}C{-}OH$, and F^+ denotes $COOH\cdots\text{-}OH{-}CH_2$. [d] Interaction distance between H-bond hydrogen atom and H-bond acceptor atom (in Å). [e] Electron density and its Laplacian calculated at BCPs, in atomic units.

Noguera et al. located six stable conformations (SerH$^+$ 1−SerH$^+$ 6) from optimizations of protonated species of eight stable neutral serine conformations obtained by approach described in method section.[24] SerH$^+$ 1−SerH$^+$ 6 correspond to **1**, **2**, **3**, **4**, **5**, **12**, respectively, in this study (conformer numbers in bold form here and in this section correspond to the column head no. listed in Table 3). Again this simpler approach is demonstrated able to identify lowest conformations of protonated species of amino acids. As listed in Table 3, six types of H-bonds were identified within framework of AIM theory, they are as follows: A^+ is $NH_3\cdots O(H)\text{-}C{=}O$, B^+ is $NH_3\cdots O{=}C{-}OH$, C^+ is $NH_3\cdots OH{-}CH_2$, D^+ is $CH_2{-}OH\cdots O(H)\text{-}C{=}O$, E^+ is $CH_2OH\cdots O{=}C{-}OH$, and F^+ is $COOH\cdots OH{-}CH_2$. In the protonated serine, nitrogen atom of the amino group is saturated by valence and can no longer act as proton acceptor. It is apparent that protonation on nitrogen makes it a stronger H-bond donor, when compared with the situation in neutral serine, in which nitrogen is unable to serve as H-bond donor. Totally, there are two A^+, nine B^+, six C^+, one D^+, one E^+, and one F^+ H-bonds existing in the conformers of serineH$^+$ (see Figure 3 for sample conformer of each bond type).

Their different average ρ_b values and average interaction distances quantitatively indicate the relative average strengths of six types. The obtained order is $F^+ > B^+ > C^+ > A^+ > E^+ > D^+$ (the average data are not shown). Again the calculated ρ_b values have excellent correlation with interaction distances (linear correlation coefficient amounts to 0.99).



A^+, C^+ (3) B^+, C^+ (1)

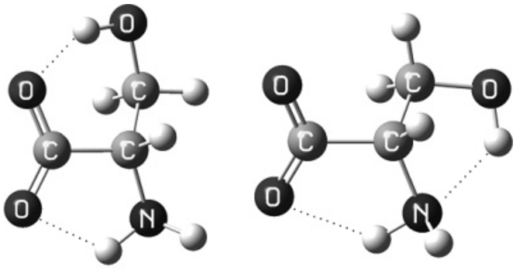
B^+, D^+ (5) A^+, E^+ (12)

Figure 3. Sample conformers optimized at B3LYP/6-311+G** level. Each represents one or two types of H-bonds, which are illustrated with dashed line. The number in parentheses (corresponding to the column head no. in Table 3) indicates the conformer in which hydrogen bonds exist.

TABLE 4: Calculated Relative Energies, Interaction Distances and Selected Topological Properties at BCPs for Conformers of Deprotonated Serine (serine$^-$)

	relative energy[a]						
no.	6-31+G*	6-311+G**	n[b]	bond[c]	distance[d]	ρ_b[e]	$\nabla^2\rho_b$[e]
1	0.00	0.00	2	C^-	2.063	0.0245	0.0929
				A^-	1.763	0.0425	0.1239
2	0.12	0.07	2	C^-	2.204	0.0199	0.0780
				A^-	1.723	0.0466	0.1302
3	2.05	1.91	1	A^-	1.766	0.0424	0.1242
4	3.08	2.99	2	C^-	2.105	0.0233	0.0862
				B^-	2.099	0.0247	0.0825
5	4.10	4.01	1	A^-	1.819	0.0369	0.1110
6	5.14	5.09	2	A^-	1.836	0.0357	0.1129
				C^-	2.151	0.0207	0.0838
7	5.43	5.38	2	C^-	1.990	0.0282	0.1039
				B^-	2.018	0.0289	0.0918
8	7.62	7.56	1	C^-	2.071	0.0241	0.0910
9	9.04	9.01	1	C^-	2.060	0.0247	0.0944
10	9.99	9.97	1	C^-	2.095	0.0231	0.0886
11	10.08	10.06	1	C^-	2.077	0.0239	0.0920

[a] 6-31G*, 6-311+G** denote relative energies calculated at B3LYP/6-311+G**//B3LYP/6-31G*, and B3LYP/6-311+G**//B3LYP/6-311+G**, respectively (in kcal/mol). [b] n denotes number of hydrogen bonds found in the conformer. [c] Three types of H-bond were found in serine$^-$ conformers: A^- denotes $CH_2OH\cdots O{-}C{=}O$, B^- denotes $CH_2OH\cdots NH_2$, and C^- denotes $NH_2\cdots O{-}C{=}O$. [d] Interaction distance between H-bond hydrogen atom and H-bond acceptor atom (in Å). [e] Electron density and its Laplacian calculated at BCPs, in atomic units.



A^-, C^- (1) B^-, C^- (4)

Figure 4. Sample conformers optimized at B3LYP/6-311+G** level. Each represents one or two types of hydrogen bonds, which are illustrated with dashed line. The number in parentheses (corresponding to the column head no. in Table 4) indicates the conformer in which hydrogen bonds exist.

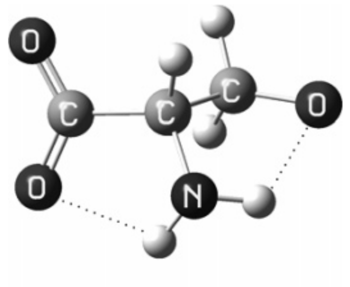
Among the 14 unique conformations, each conformer contains one or two intramolecular H-bonds, except for the highest 2 conformers. This further supports the conclusion that intramolecular H-bond is a key factor in the relative stability of amino acids and its relative ions.

Interaction distances ($r_{H\cdots X}$) optimized at B3LYP/6-31G* and topological parameters at BCPs of H-bonds calculated at B3LYP/6-311+G**//B3LYP/6-31G* level are listed in Table S2. B3LYP/6-31G* geometries agree well with B3LYP/6-311+G** geometries not only on the covalence bond lengths but also on most of the interactions distances of intramolecular H-bonds. The calculated average difference in interaction distances is merely ca. 0.03 Å. Furthermore, the intramolecular bonding schemes predicted at these two levels are also in general consistence. Thus, B3LYP/6-31G* geometries could reliably be used in thermochemical calculation and investigation of intramolecular H-bonds for protonated species of amino acids.

3.3. Serine$^-$. Considering the strong acidity, the favorable deprotonation site of serine should be at carboxylic group. In the geometry optimizations for serine$^-$, 162 possible conformations were optimized due to lacking of single-bond rotor **a** with respect to serine and serineH$^+$, and 11 conformations were located at B3LYP/6-31G* level. Further refinement at B3LYP/6-311+G** level did not change the total number of conformations, and these 11 unique conformations were confirmed by frequency analysis to be energy-minima on PES of serine$^-$. The energies of obtained 11 unique conformations vary by ca. 10 kcal/mol. The relative energies calculated at B3LYP/6-311+G**//B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-311+G** level are both listed in Table 4. And again B3LYP/6-311+G**//B3LYP/6-31G* provides an energetic result similar to that predicted at the B3LYP/6-311+G**//B3LYP/6-311+G** level.

Three types of H-bond were identified within AIM theory among 11 serine$^-$ conformers, they are A^- is $CH_2OH\cdots O{-}C{=}O$, B^- is $CH_2OH\cdots NH_2$, and C^- is $NH_2\cdots O{-}C{=}O$ (see Figure 4 for sample conformer of each bond type). The order of relative strength of H-bonds based on average values of ρ_b is $A^- > B^- > C^-$. Owing to the anionic form of the carboxyl group, it can be expected that two oxygen atoms should obtain a considerable gain in electron density and serve as a stronger H-bond acceptor. The average ρ_b value of type A^- is notably larger than the other two types (0.0408, 0.0268, and 0.0236 for A^-, B^-, C^-, respectively), and average interaction distance is also much shorter (1.781, 2.059, and 2.091 Å for A^-, B^-, C^-, respectively). The geometric factor also favors the type A H-bond: type A involves a six-membered ring, while the other two involve five-membered rings.

Among the 11 conformers, the highest 4 conformers contain only the weakest C^- bond, while the lowest conformations tend to contain stronger A^- or B^- bonds. This further supports that



A²⁻, B²⁻ (1)

Figure 5. Sample conformers optimized at B3LYP/6-311+G** level, representing two types of H-bonds, which are illustrated with dashed line. Number in parentheses (corresponding to the column head no. in Table 5) indicates the conformer in which hydrogen bonds exist.

TABLE 5: Calculated Relative Energies, Interaction Distances and Selected Topological Properties at BCPs for Conformers of Deprotonated Serine (serine^{2-})

	relative energy[a]						
no.	6-31G*	6-311+G**	n[b]	bond[c]	distance[d]	ρ_b[e]	$\nabla^2\rho_b$[e]
1	0.00	0.00	2	A^{2-}	2.143	0.0216	0.0745
				B^{2-}	2.217	0.0187	0.0745
2	3.49	3.61	2	A^{2-}	1.998	0.0279	0.0949
				B^{2-}	2.101	0.0230	0.0851
3	6.33	6.37	0				
4	8.96	8.97	1	B^{2-}	2.106	0.0226	0.0877

[a] 6-31G*, 6-311+G** denote relative energies calculated at B3LYP/6-311+G**//B3LYP/6-31G*, and B3LYP/6-311+G**//B3LYP/6-311+G**, respectively (in kcal/mol). [b] n denotes the number of hydrogen bonds found in the conformer. [c] Two types of H-bond were found in serine^{2-} conformers: A^{2-} denotes $NH_2\cdots O-CH_2$, and B^{2-} denotes $NH_2\cdots O-C{=}O$. [d] Interaction distance between H-bond hydrogen atom and H-bond acceptor atom (in Å). [e] Electron density and its Laplacian calculated at BCPs, in atomic units.

hydrogen bond is one of the major contributive factors in the relative stability of conformers.

Interaction distances ($r_{H\cdots X}$) optimized at B3LYP/6-31G* level and topological parameters at BCPs of H-bonds calculated at B3LYP/6-311+G**//B3LYP/6-31G* level are gathered in Table S3. While these levels provide similar bond lengths for covalence bonds, B3LYP/6-31G* geometries differ appreciably from B3LYP/6-311+G** geometries in geometric parameters of H-bonds (average difference is ca. 0.07 Å). Nevertheless, in accordance with the results of the conformers of neutral serine, the most important features of the energy, structure, and intramolecular bonding scheme are recovered at B3LYP/6-311+G**//B3LYP/6-31G* level.

3.4. Serine^{2-}. Deprotonation of the second proton from serine$^-$, which occurs at the side-chain OH group, plays an important role in understanding biological functions and chemistry of serine in peptides and proteins. The deprotonation of side-chain OH group in serine functions as a catalytic site in certain serine-containing peptidases. Because of removal of two protons, only three single-bond rotors remain in serine^{2-} (see Scheme 1). Therefore, 54 trial structures were fully optimized, and 7 conformations were obtained at B3LYP/6-31G* level. Further refinement at B3LYP/6-311+G** level led to 4 unique conformations, which were confirmed by frequency analysis to be energy minima on PES of serine^{2-}. The energies of obtained 4 conformations vary by ca. 9 kcal/mol. The relative energies calculated at B3LYP/6-311+G**//B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-311+G** level are both listed in Table 5. The results obtained at these two levels are in general accordance with each other.

The complexity significantly decreases in conformers of serine^{2-} due to deprotonation of two protons. Nitrogen atom turns to be the only H-bond donor and two anionic groups (carboxyl and hydroxyl groups) serve as acceptor. Indicated by the average values of ρ_b and interaction distances, type A^{2-} is stronger than B^{2-} (average values of ρ_b are 0.0247 and 0.0214 for A^{2-} and B^{2-}, interaction distances are 2.071 Å and 2.141 Å for A^{2-} and B^{2-}, respectively). Both of these two bond types involve five-membered ring structure and oxygen as H-bond acceptor. However, delocalization of negative charge to the whole carboxyl anion group (COO^-) decreases the electron density on carbonyl oxygen and consequently makes it an H-bond acceptor not as strong as hydroxyl anion. This is reflected by their atomic charge: carbonyl O is ca. −0.9 e; hydroxyl O is ca. −1.2 e (Merz−Kollman[50] charge calculated at B3LYP/6-311+G** level using B3LYP/6-311+G** geometry).

Within the four conformers of serine^{2-}, the lowest two conformers contain two H-bonds and both of them have stronger type A^{2-} whereas the highest two conformers do not contain H-bond or contain one weaker type B^{2-} H-bond.

Interaction distances ($r_{H\cdots X}$) optimized at B3LYP/6-31G* level and topological parameters of BCPs calculated at B3LYP/6-311+G**//B3LYP/6-31G* level are gathered in Table S4. B3LYP/6-31G* geometries exhibit noticeable difference from B3LYP/6-311+G** geometries principally in geometric parameters of H-bonds. The average difference in interaction distances amounts to ca. 0.1 Å, which is the largest among calculations of serine and related ions. Furthermore, it is noticed that conformer **3** (corresponding to conformer **3** in Table S4) does not form an H-bond with B3LYP/6-311+G** geometry, whereas one H-bond was identified with B3LYP/6-31G* geometry. This variation may result from the lack of diffuse functions, which are always considered to be important for calculation of anionic species. The results indicate that B3LYP/6-31G* geometry can roughly approximate the geometry of B3LYP/6-311+G** level; however, if high accuracy is desired, a large basis set with diffuse functions should be used for calculation of anionic species containing intramolecular H-bonds.

3.5. Gas-Phase Thermodynamic Properties of Serine and Its Related Ions. Proton affinity is calculated as the negative of the enthalpy change of the protonation reaction (A) of serine, the negative of the Gibbs energy change associated with the protonation reaction (A) is the gas-phase basicity. Proton dissociation energy is the enthalpy changes of the deprotonation reaction (B) and (C), gas-phase acidity is the Gibbs energy change ($\Delta G = \Delta H - T\Delta S$). The three chemical reactions used are

$$\text{serine} + H^+ \rightarrow \text{serineH}^+ \quad \text{(A)}$$

$$\text{serine} - H^+ \rightarrow \text{serine}^- \quad \text{(B)}$$

$$\text{serine}^- - H^+ \rightarrow \text{serine}^{2-} \quad \text{(C)}$$

The theoretical values were obtained from the calculations of the most stable conformers of the each species, since the conformational equilibrium effect (CEE) correction has been shown to lead to an indiscernible difference.[33] The calculated results obtained at B3LYP/6-311+G**//B3LYP/6-31G* (thermal corrections were calculated at B3LYP/6-31G* level) and B3LYP/6-311+G**//B3LYP/6-311+G** level were both listed in Table 6.

The calculated $-\Delta H$ and $-\Delta G$ for reaction A at two levels, as shown in Table 5, are both in excellent agreement with

TABLE 6: Calculated Proton Affinity/Proton Dissociation Energy and Gas-Phase Basicity/Acidity for the Serine and Its Related Ions

	proton affinity/proton dissociation energy[a]		gas-phase basicity/acidity[a]	
reaction	calcd[b]	expt[c]	calcd[b]	expt[c]
A	217.8[d]	218.6	210.0	210.5
	217.8[e]		*209.7*	
B	330.2	332.7 ± 3.1	323.1	325.8 ± 3.0
	330.4		*323.5*	
C	454.9		447.1	
	455.4		*447.7*	

[a] Calculated energies are in kcal/mol. [b] Single-point electronic energies were all calculated at B3LYP/6-311+G**. All the thermochemical data correspond to the reference state of 1 atm, 298 K. [c] Experimental data were taken from NIST.[29,35,51] [d] Values calculated using B3LYP/6-311+G** geometries, the energy correction to enthalpy and free energy were obtained at B3LYP/6-311+G** level (unscaled). [e] Values calculated using B3LYP/6-31G* geometries (in *italic* form), the energy correction to enthalpy and free energy were obtained at B3LYP/6-31G* level (unscaled).

experimental data; both with a deviation of less than 1 kcal/mol. Previous theoretical results at the MP2 level using HF geometries provide proton affinity value of 216.0 kcal/mol for serine,[34] showing larger deviation from the experimental value. This suggests that calculation method used in optimization should include the electron correlation. Calculations done by Noguera et al.[24] also using DFT method (B3LYP/D95++(d,p)) provide results very close to experimental values (218.3 and 210.6 kcal/mol for proton affinity and gas-phase basicity, respectively). Calculated ΔH and ΔG for reaction (B) are also in good agreement with experimental values, both falling well in the range of experimental error. Reaction C has no experimental data for comparison to date, but we are confident of the accuracy of theoretical values obtained, since the applicability of our approach has been approved in calculations of reactions A and B. The two approachs used in this study (B3LYP/6-311+G**//B3LYP/6-31G* and B3LYP/6-311+G**// B3LYP/6-311+G**) are both able to provide results with excellent accuracy. This indicates that B3LYP/6-31G* geometry together with higher level energy calculation could provide theoretical thermodynamic parameters of amino acids and the related ions with acceptable accuracy. Considering the relatively low computational cost of B3LYP in comparison with traditional correlated methods (MP2, MP4, etc.) and its medium-size basis set (6-31G*), it would be considered as a practical method for calculating gas-phase thermodynamic properties for larger amino acids, peptides or their derivatives.

4. Conclusion

Conformational study of serine has been demonstrated to be highly complex due to its added molecular size and the side chain of hydroxyl group, which is able to act as H-bond donor and acceptor. With a view to taking a comprehensive study of conformations of serine and its related ions at high-level calculation, a full ensemble of possible conformations, i.e., 324 for neutral serine, 108 for serineH$^+$, 162 for serine$^-$ and 54 for serine^{2-} has been optimized at the B3LYP/6-31G* level and then refined at the B3LYP/6-311+G** level. In total, 74 unique conformations for neutral serine, 14 for serineH$^+$, 11 for serine$^-$, and 4 for serine^{2-} were identified. AIM analyses of these conformations were performed and established a rigorous definition of intramolecular hydrogen bonds. Intramolecular hydrogen bonds defined within the framework of AIM theory have been shown to play an important role in deciding the relative stability of conformation of serine and its related ions in the gas phase. The relative strengths of the intramolecular hydrogen bonds were also determined based on average values of ρ_b and interaction distances.

The calculated proton affinities/proton dissociation energies and gas-phase basicities/acidities of serine and its related ions in gas phase are in excellent agreement with experimental data. The DFT (B3LYP) method is demonstrated to be able to provide accurate structural and energetic descriptions of amino acid and related ions. B3LYP/6-31G* geometry combined with higher-level energy calculation is found to be able to provide good theoretical results of gas-phase thermodynamic parameters of amino acids and the related ions, and B3LYP/6-31G* geometry is able to recover the most important geometric and intramolecular bonding features of amino acids. Considering its relative low computational cost in comparison with other traditional correlated methods, B3LYP appears to be an ideal method for conformational and thermodynamic investigations of amino acids or larger biological systems such as polypeptides.

Acknowledgment. This work was supported by the National Science Foundation of China (Nos. 20271027 and 20231010).

Supporting Information Available: The calculated relative energies, interaction distances, selected topological properties at BCPs of H-bonds using B3LYP/6-31G* geometries for conformers of serine (Table S1), serineH$^+$ (Table S2), serine$^-$ (Table S3) and serine^{2-} (Table S4) and tables giving the optimized geometries of all conformers of serine and its related ions studied in this report (83 structures for serine, 21 for serineH$^+$, 11 for serine$^-$ and 7 for serine^{2-} at B3LYP/6-31G* level; 74 structures for serine, 14 for serineH$^+$, 11 for serine$^-$, and 4 for serine^{2-} at B3LYP/6-311+G** level). This material is available free of charge via the Internet at http://pubs.acs.org.

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