PAPER

NJC
www.rsc.org/njc

The regulatory roles of metal ions ($M^{+/2+} = Li^+, Na^+, K^+, Be^{2+}, Mg^{2+}$, and Ca^{2+}) and water molecules in stabilizing the zwitterionic form of glycine derivatives†

Hongqi Ai,[ab] **Yuxiang Bu,***[b] **Ping Li**[b] **and Chong Zhang**[bc]

[a] *School of Chemistry and Chemical Engineering, Jinan University, Jinan, 250022, P. R. China*
[b] *Institute of Theoretical Chemistry, Shandong University, Jinan, 250100, P. R. China. E-mail: byx@sdu.edu.cn*
[c] *Department of chemistry and technology, Liaocheng University, Liaocheng, 252059, P. R. China*

Received (in Montpellier, France) 5th July 2005, Accepted 6th October 2005
First published as an Advance Article on the web 24th October 2005

The regulatory roles of metal ions ($M^{+/2+} = Li^+, Na^+, K^+, Be^{2+}, Mg^{2+}$, and Ca^{2+}) and water molecules in stabilizing the zwitterionic form of glycine derivatives are discussed in the present paper. The involved glycine conformers are (1) the glycine zwitterion (OO), which can bind an ion to form the salt-bridge-form derivative, and (2) two neutral forms (NO and OH), which can bind the ion with both the carboxyl oxygen and the amino nitrogen (NO), or both the carboxyl oxygen and the hydroxyl oxygen (OH) to form charge-solvated structures. Results show that four water molecules can make the OO-mode glycine–$Li^+/Na^+/K^+$ derivatives more stable than each of the corresponding NO-mode counterparts. Similarly, two water molecules can make the OO-mode glycine–Be^{2+} more stable than its corresponding NO-mode counterpart, while the OO-mode glycine–Mg^{2+}/Ca^{2+} are always more stable than their corresponding NO counterparts whether there is a water molecule(s) attached or not. No OH-mode glycine–$Be^{2+}/Mg^{2+}/Ca^{2+}$ hydrates are observed because the large electrostatic effect of these divalent metal ions makes the OH-mode hydrates degenerate into the OO-mode ones. For the non-hydrated or monohydrated glycine–Li^+/Na^+ isomers, the global minimum derives from the NO-mode structure. Their (di–tetra)hydrates, however, prefer the OH-mode to the other two. For all these different glycine–K^+ hydrates, each OH-mode structure is always the global minimum among the corresponding isomers, as for the non-hydrated reactant (glycine–K^+). These predictions are consistent with other theoretical and experimental results. Most of the relative binding strengths, between a metal ion and its corresponding ligand, of the three modes are in good agreement with the relative stabilities, *i.e.*, the larger the binding energy is, the more stable the structure would be. Some exceptions to the agreement are explained. A comparison of binding strengths shows that the smaller the ion radius is, the greater its binding strength would be. For instance, Li–NO · W (-50.5 kcal mol^{-1}) > Na–NO · W (-36.4 kcal mol^{-1}) > K–NO · W (-25.4 kcal mol^{-1}).

1. Introduction

Amino acids and peptides form the building blocks of proteins. Among biomolecules, peptides are unique in having seemingly infinite conformational possibilities and a broad spectrum of functional groups. 3-Dimensional structural information on simpler species such as isolated amino acids[1,2] is very important for a good understanding of peptides and proteins.

It is known that amino acids in solution exist predominately as zwitterions at pH 7, with the carboxyl deprotonated and one of the nitrogen atoms protonated, and the most stable form of isolated amino acids in the gas phase is non-zwitterionic. As the simplest amino acid, glycine has been extensively studied by theoretical and experimental methods.[3–18] The non-zwitterionic form is calculated to be 19.3 kcal mol^{-1} more stable than the zwitterionic form.[3] Both microwave experiments[19] and gas-phase basicity measurements[20] have demonstrated that glycine is not a zwitterion in the gas phase. Due to the importance of information about the gas-phase intrinsic properties for the solution-phase measurements,[21] a number of attempts have been made at stabilizing and characterizing the gas-phase zwitterions. These efforts have concentrated on the hydrated,[22–24] or the metal-ion cationized zwitterionic systems,[25–29] *etc.* For the hydration of the zwitterionic glycine, Jensen *et al.*[30] have determined that two water molecules can stabilize the glycine zwitterion. Metal cationization can not only stabilize zwitterionic systems[25–29] but can also result in many biological functions. For example, the osmotic equilibrium of cells, the electrical excitability of nerves and muscles, the active transport of glucides and amino acids all involve the alkali metal cations. Moreover, the formation of polypeptides from amino acids can be enhanced by the presence of divalent alkali earth metal cations.[31] It is known that the sodium (Na^+), potassium (K^+), magnesium (Mg^{2+}) and calcium (Ca^{2+}) cations are the most familiar cations *in vivo*, with various functions, such as those in Na-, K-ATPase[32] and the calcium pump,[33] *etc.*

For these metallized glycine derivatives, many papers[25,31,34] have implied that two modes would be preferred for the binding of a metal cation by a glycine molecule. They are that the cation is bound (1) to both the N3 and O5 sites of the neutral glycine (NO mode), or (2) to both oxygens of the

---

† Electronic supplementary information (ESI) available: HF-optimized structures and B3LYP-refined relative energies of each isomer series for the M–NO/OO/OH · *n*W complexes (n = 0–4 for $M^+ = Li^+$, Na^+, or K^+, and n = 0–2 for $M^{2+} = Be^{2+}$, Mg^{2+}, or Ca^{2+}) are displayed in Fig. S1–S4. The B3LYP-optimized NBO charge populations over the different metal cations in these complexes are listed in Table S1. See DOI: 10.1039/b509496h

DOI: 10.1039/b509496h

zwitterionic glycine (OO mode). Only glycine–K^+ derivatives have the lowest-energy structure with the OH mode, in which the K^+ is coordinated to both the carbonyl oxygen and hydroxyl oxygen (see Fig. 1). A special study on the combination modes from Hoyau *et al.*[35] confirmed this point. For the monovalent cations, the product with the OO mode is a local minimum, not the global one on its potential energy surface (PES),[25,26,28] while the same product form in some divalent metal cationized systems becomes the global minimum on the PES. In these interactions, the electrostatic effect between the glycine and the metal ion plays a significant role, especially for the divalent metal-ion coupled systems.[27–29]

Because of the importance of the solvent effect *in vivo*, an investigation into the most stable form of cationized glycine in aqueous solution would be important for one to understand the optimal coordinate form of a cation to the protein ligand *in vivo*. The interaction modes and energies between water molecules and some cationized amino acids have been partially investigated previously.[36–38] Different from these studies, the purpose of this research is to carry out a detailed investigation of the number of attached water molecules required to stabilize the OO-mode glycine–$M^{+/2+}$ ($M^{+/2+} = Li^+$, Na^+, K^+, and Be^{2+}, Mg^{2+}, and Ca^{2+}) over its NO-mode counterpart so that the preferred mode in the solvent can be determined.

2. Computational methods

Starting structures for these M–NO/OO/OH·*n*W complexes (W = water) are generated using the different metal cations to bind both the amino nitrogen and the carbonyl oxygen, two bare carbonyl oxygens, or both the carbonyl oxygen and the hydroxyl oxygen of the glycines, and then n ($n = 0$–4) water molecules are attached. For the cationized glycine derivatives in the gas phase, their lowest-energy structures would have either the NO or the OO mode, with the exception of glycine–K^+ with the OH mode,[25,28,35] thus their lowest-energy hydrates would be expected to be derived from these modes. The prediction had been confirmed by Benzakour *et al.*,[36] Williams *et al.*[37] and Armentrout *et al.*[38] Clearly, these lowest-energy hydrates should be the best candidates to study various properties of the hydrated systems. However, the search for each lowest-energy hydrate is complicated and difficult. Thus various possible isomers of each hydrate were designed and optimized and the results are given in the present paper. In the six different metal ion-involved systems, the definition of each complex has the metal-ion (M) name as a prefix to distinguish them. For example, Na–NO·W denotes the NO-mode monohydrates involving Na^+. K–NO/OO/OH·2W and Li/Na–NO·3W are the abbreviations of three dihydrates, K–NO·2W, K–OO·2W and K–OH·2W, and of two trihydrates, Li–NO·3W and Na–NO·3W, respectively.

For all these M–NO/OO/OH·*n*W complexes, the geometries, frequencies and zero point vibrational energies (ZPVE) were determined first at the HF/6-31G* level, then the single point calculations were performed at the B3LYP/6-311+G* level[39] so that each most stable hydrate could be distinguished from their various isomers exactly. Refined optimizations on the most stable NO-, OO- and OH-mode structures of each hydrate series have been performed at the B3LYP/6-31G** level. Natural bond orbital (NBO) analyses of charges were also carried out at the level. Their relative energies and electronic binding energies have been single-point-calculated with the 6-311+G(2d,2p) basis set at both the B3LYP and MP2 levels,[40] respectively. The basis set superposition errors (BSSEs)[41] have been taken into account at the same levels to correct all binding energies. The following discussions are mainly based on these B3LYP data except where specified to be different. MP2 results are mainly employed to verify or compare with these B3LYP-data.

The electronic binding energy of the complex in a given coordination structure is defined as:

$$\Delta E = E_C - E_1 - E_2 \qquad (1)$$

Where E_C, E_1 and E_2 denote the energies of the optimized M–NO/OO/OH·*n*W complexes, and two corresponding reactants—NO/OO/OH·*m*W glycine species (*i.e.*, without a metal ion) and the $(n - m)$W·M species ($0 \le m \le n \le 4$), respectively.

All calculations are performed with the GAUSSIAN 98 package of programs.[42]

3. Results and discussion

3.1 The search and comparison of the most stable structures of each hydrate

3.1.1 Glycine–Li^+/Na^+/K^+ and their hydrates. Fig. 1 lists B3LYP/6-31G**-optimized (mono–tetra)hydrates of glycine–M^+ ($M^+ = Li^+$, Na^+, K^+) and (mono–di)hydrates of glycine–M^{2+} ($M^{2+} = Be^{2+}$, Mg^{2+}, Ca^{2+}), including their most stable gas-phase structures. Table 1 reports the relative energies of these complexes. As reported previously,[24,25] the glycine–Li^+/Na^+ derivatives have the NO-mode ground-state structure, while the OO-mode structure is predominant in aqueous solution but several kcal mol^{-1} higher than the NO-mode energy in the gas phase. K–OH is the ground state[25] of those K cationized glycine isomers and the OH mode can produce more stable hydrates for the glycine–Li^+/Na^+ complexes[36,38] (see M–NO/OO and Li/Na/K–OH in Fig. 1). Thus the three different binding modes (OH/NO/OO) are selected. All of their hydration schemes (SCHs) are given in Fig. 2. The OO mode in Fig. 1 is divided into two types in Fig. 2, OO1 and OO2 modes, according to their different amino-hydrogen(s) orientations. For the monovalent cationized[25,34*a*,*d*] derivatives of zwitterionic glycine, M–OO1, with only one amino hydrogen pointing to the carbon oxygen, is preferred, while the divalent alkali-earth-metal and transition-metal cationized ones prefer the M–OO2 structure with two bifurcated amino hydrogens pointing to the carbon oxygen.[26,31,34*a*,*b*] Both the monovalent alkali-metal and the Be^{2+} cationized OO modes are less stable than their NO-mode counterparts in the gas phase.[26,34*a*] It is known that the glycine zwitterion predominates in aqueous solution and the metallized glycine derivatives are also common *in vivo*. As part of investigations to probe the hydration effect on the stability of these metallized glycine derivatives with different modes, it had previously been found that OO1-mode dihydrated glycine–Zn^+ is more stable than the NO-mode counterpart.[27] The study confirmed that the solvent effect is more favorable for the stability of the OO1-mode glycine derivatives cationized by a monovalent transition metal ion. Then what about those alkali and alkali-earth metal cationized OO-mode structures? Here we discuss these questions beginning with the Li^+/Na^+/K^+-involved systems.

For the most stable NO/OO/OH-mode glycine–Li^+/Na^+/K^+ derivatives, any of them would produce several different monohydrate isomers when a water molecule is bound to their different active sites (see M–NO·W, M–OO1·W and M–OH·W in Fig. 2). Among them, the metal ion would be preferred due to the largest electrostatic effect at the site (SCH-I in Fig. 2).[27*a*] For the OO1/OH modes, either an amino/hydroxyl hydrogen (SCH-II or III) or metal ion (SCH-I) can be attacked by a water molecule. The two C_α hydrogens ($-CH_2-$) in glycine, however, would be difficult to attach to a water molecule.[27] The HF-optimized structures of these hydrates and their relative energies are listed in Fig. S1–S3 of the ESI.† The structures of those alkali-earth metallized glycine multihydrates and the relative energies of each corresponding isomer series are listed in Fig. S4 of the ESI. Table S1 in the ESI collects the B3LYP/6-31(d,p)-calculated NBO charge populations over each metal ion in these different complexes. Only the

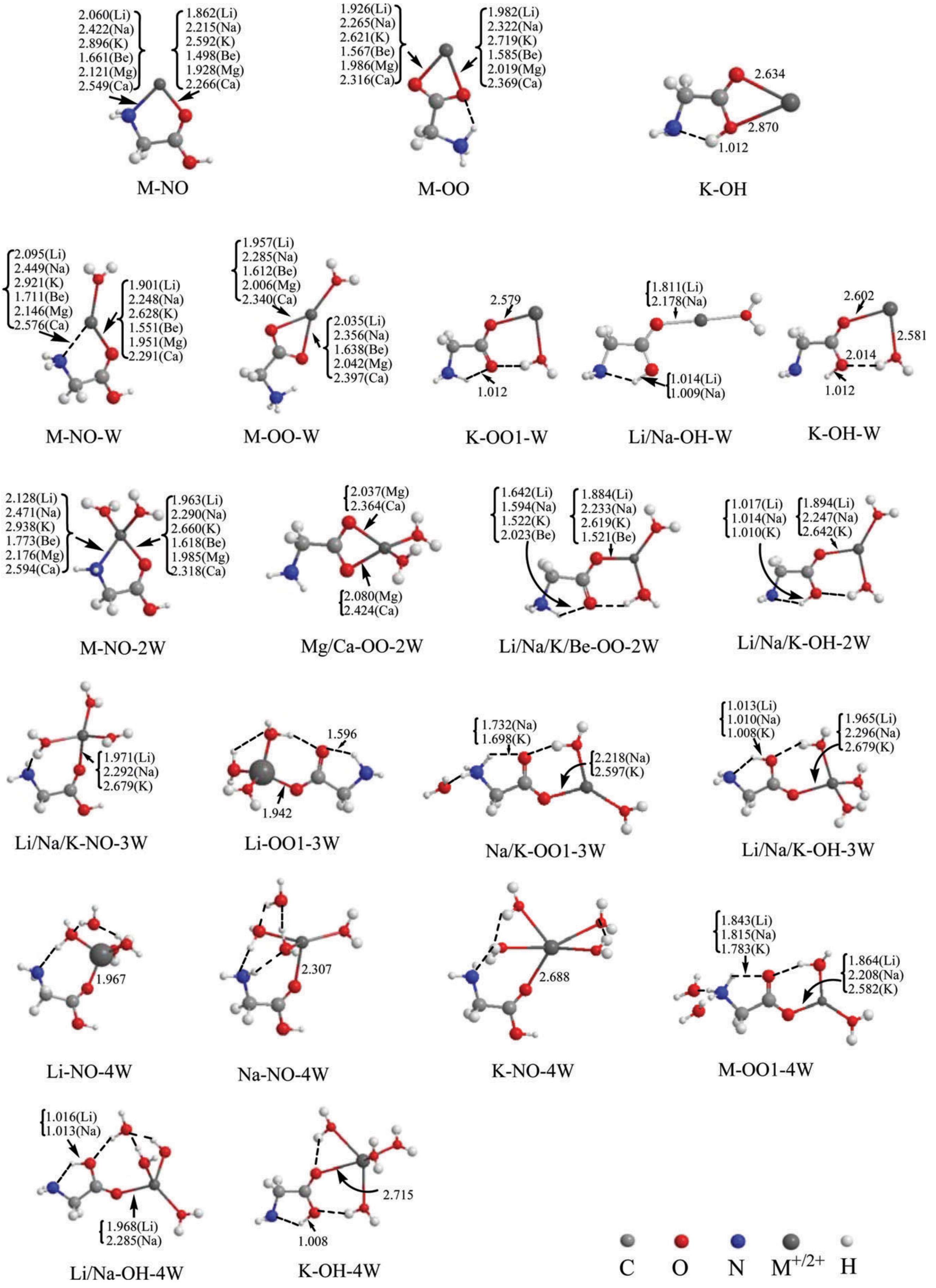

Fig. 1 B3LYP/6-31G**-optimized (mono–tetra)hydrates of glycine–M^+ ($M^+ = Li^+$, Na^+, K^+) and (mono–di)hydrates of glycine–M^{2+} ($M^{2+} = Be^{2+}$, Mg^{2+}, Ca^{2+}), including their gas-phase states. Hydrogen bonding is shown with broken lines (--). Those structures which differ drastically and cannot be denoted by the general form M–XX · *n*W, are drawn separately. Distances in Å.

Table 1 ZPVE-corrected relative energies (kcal mol^{-1}) of the M–OO/NO $\cdot$ nW^{a} complexes relative to their M–OH $\cdot$ nW (n = 0–4, M = Li, Na or K) counterparts (entries 1–15) and of the OO-mode complexes relative to their NO-mode counterparts (entries 16–24) obtained at (**I**) B3LYP/6-311+G(2d,2p)//B3LYP/6-31G**, and (**II**) MP2/6-311+G(2d,2p)//B3LYP/6-31G** levels

Entry	Complex	**I** (kcal mol^{-1})	**II** (kcal mol^{-1})
1	Li–OO1/NO	−3.8/−8.7	−7.8/−10.4; [−7.5/−10.8]^{b}
2	Na–OO1/NO	−2.5/−0.2	−3.3/−2.6; [−3.8/−2.4]^{b}
3	K–OO1/NO	2.3/0.3	2.0/0.3; [1.9/0.1]^{b}
4	Li–OO1/NO $\cdot$ W	0.9/−4.3	−0.5/−5.1
5	Na–OO1/NO $\cdot$ W	1.7/−1.3,	1.9/1.8 [−1.9]^{ef}
6	K–OO1/NO $\cdot$ W	3.0/2.3	2.8/2.4
7	Li–OO1/NO $\cdot$ 2W	2.4/0.4; [1.6/0.2]^{d}	1.9/−0.6
8	Na–OO1/NO $\cdot$ 2W	1.5/0.5	0.2/—
9	K–OO1/NO $\cdot$ 2W	3.9/4.1	3.6/3.0
10	Li–OO1/NO $\cdot$ 3W	3.5/1.0; [3.4/1.2]^{d}	3.1/1.3
11	Na–OO1/NO $\cdot$ 3W	3.2/1.8,	0.7/0.5
12	K–OO1/NO $\cdot$ 3W	2.6/1.7	2.4/1.4
13	Li–OO1/NO $\cdot$ 4W	0.1/2.6	1.4/3.4
14	Na–OO1/NO $\cdot$ 4W	1.2/2.3,	0.2/1.9
15	K–OO1/NO $\cdot$ 4W	1.2/2.5	1.8/2.1
16	Be–OO2	6.5, 6.5^{c}	4.4
17	Mg–OO2	−7.9, −6.9^{c}	−10.0
18	Ca–OO2	−12.3, −9.2^{c}	−13.4
19	Be–OO2 $\cdot$ W	2.8	1.4
20	Mg–OO2 $\cdot$ W	−6.8	−8.7
21	Ca–OO2 $\cdot$ W	−10.5	−11.4
22	Be–OO2 $\cdot$ 2W	−5.4	−3.8
23	Mg–OO2 $\cdot$ 2W	−5.9	−7.3
24	Ca–OO2 $\cdot$ 2W	−9.0	−9.9

[a] M–OO/NO $\cdot$ nW is the abbreviation of M–OO $\cdot$ nW and M–NO $\cdot$ nW complexes. [b] From ref. 25 obtained at the MP2/6-31G* level. [c] From ref. 46 obtained at the B3LYP/LACVP+(d,p) level. [d] From ref. 36 obtained at the B3LYP/6-311++G(d,p) level. [e] The value is obtained at the MP2(full)/6-311++G(d,p)//B3LYP/6-31G** level. [f] No energies of Be/Mg/Ca–OH $\cdot$ nW are displayed in the table because the strong electronic effect of the divalent metal ions makes the their OH-mode structures turn into the OO2-mode ones.[25,46]

most stable structures, with selected parameters of each mode obtained and with refined optimization at the B3LYP/6-31G** level are displayed in Fig. 1 and discussed in the present paper. Relative energies displayed in Fig. S1–S3 and Table 1 show that Li/Na–NO $\cdot$ W in Fig. 1 are the lowest energy tautomers of these monohydrated glycine–Li^{+}/Na^{+} complexes, consistent with the conclusions of Lemoff *et al.*[37] and Ye *et al.*[38] Our calculations for the K^{+}-involved system show that K–OH $\cdot$ W is still the lowest energy structure among its isomers. Li–OO1/OH $\cdot$ W and Na–OO1/OH $\cdot$ W are 5.2/4.3 and 3.0/1.3 kcal mol^{-1} over their corresponding NO-mode counterparts in energy, respectively. Reoptimization at the B3LYP/6-311++G(d,p) level also confirms the above energy ordering. These indicate that monohydration at the metal ion end does not improve the stability of the Li/Na–OO1 $\cdot$ W complexes over their Li/Na–NO $\cdot$ W counterparts, and also does not change the relative stability of the three different-mode (OH/NO/OO1) glycine–K^{+} derivatives.

The selections of computational methods and structures of glycine–M^{+} reactants benefit from the work of the predecessors,[25,36–38] and some important information from these works has been considered. At the level of MP2/6-311+G(2d,2p)//B3LYP/6-31G**, for example, Li–OO1/NO and Na–OO1/NO are 7.8/10.4 and 3.3/2.6 kcal mol^{-1}, respectively, more stable than each OH-mode counterpart. The identical values obtained with the MP2 method by Hoyau *et al.*[25] are 7.5/10.8 and 3.8/2.4 kcal mol^{-1}, respectively, in good agreement with our prediction. Similarly, our calculations at the MP2/6-311+G(2d,2p)//B3LYP/6-31G** level show that energies of K–OO1/NO are 2.0/0.3 kcal mol^{-1} more than that of K–OH, also consistent with that of ref. 25 (1.9/0.1 kcal mol^{-1}). The consistency of these results indicates that our treatment of the hydrates of the three modes with the same methods would be reliable.[36–38] The reliability can also be confirmed by the agreement of MP2 and B3LYP data for the relative energies of these hydrates (see Table 1) excluding three exceptions. The exceptions had also been observed by Ye *et al.* on treating these multihydrates.[38] For example, Table 1 shows that at the B3LYP level the Na–NO $\cdot$ W is 1.3 kcal mol^{-1} more stable than the OH-mode counterpart, while at the MP2 level their relative stability reverses with a difference of 1.8 kcal mol^{-1}. Another two exceptions (disagreements) are the stability ordering of Li–OO1 $\cdot$ W and Li–NO $\cdot$ 2W relative to each corresponding OH-mode. To calibrate the results, MP2(full)/6-311+G(2d,2p)//B3LYP/6-31G** calculations were performed for the Na–NO/OH $\cdot$ W energies (as an example). The results showed that Na–NO $\cdot$ W is 1.9 kcal mol^{-1} less stable than Na–OH $\cdot$ W. The ordering is in agreement with those of the B3LYP data mentioned above and of Ye *et al.* obtained at the MP2(full) level. Thus these B3LYP results would be more reliable, confirmed by another agreement between our B3LYP result (0.4 kcal mol^{-1}) for Li–NO $\cdot$ 2W (relative to the Li–OH $\cdot$ 2W) and those of Benzakour *et al.*[36] (0.2 kcal mol^{-1}, see Table 1).

On the basis of monohydrates, several cases were considered to generate the different dihydrates of the NO/OO/OH modes. For the Li/Na/K–NO, their dihydrates were obtained by (1) binding both water molecules to the metal ion end (SCH-I); or (2) binding a water molecule to the metal ion and another to the hydroxyl (SCH-II) or amino hydrogen (SCH-III). Relative to the schemes of those Li/Na/K–NO complexes, the three schemes of obtaining Li/Na/K–OO1 dihydrates do not include the NO-mode SCH-II but the scheme with dihydration at both amino hydrogens, the OO1-mode SCH-III, is included. The SCHs-I and III of the OH-mode dihydrates are similar to those of the NO-mode ones. Another two schemes are also attempted according to the structural characteristic of the mode, *i.e.*, a water molecule is bound to the hydroxyl hydrogen and another one to the metal ion (SCH-II) or an amino hydrogen (SCH-IV) (see Fig. 2 and Fig. S1–S3). It is noted that not all the schemes, but at least one, were tested for these different ion-involved systems due to the property similarity of these glycine derivatives.[25,36–38] The selection of the absent scheme in some ion-

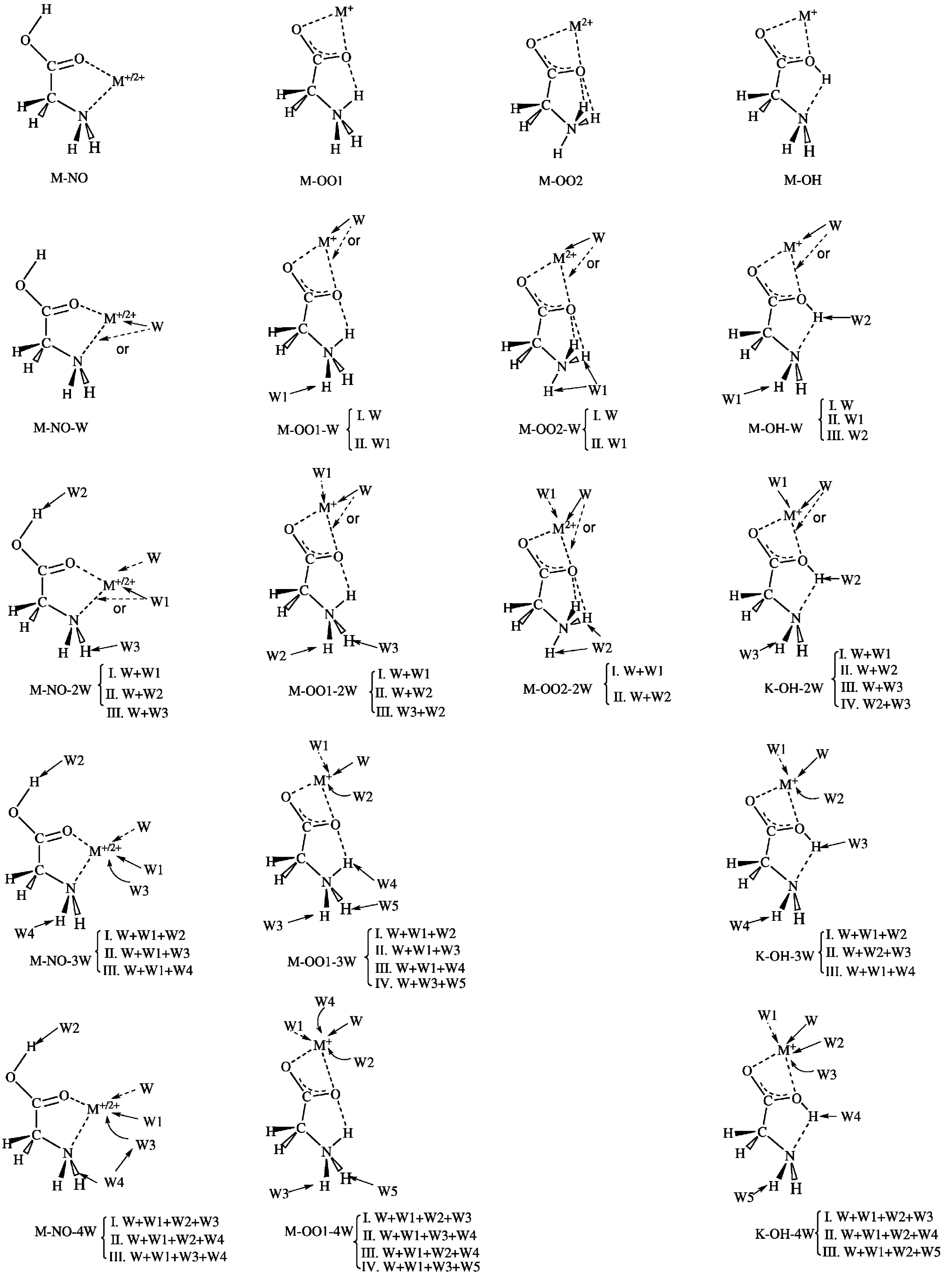

Fig. 2 Different attacking schemes of water molecules (W) to produce multihydrates (n = 0–4) of glycine–$M^{+/2+}$ [$M^+ = Li^+$, Na^+ or K^+ (1st, 2nd and 4th columns) and $M^{2+} = Be^{2+}$, Mg^{2+} or Ca^{2+} (1st and 3rd columns)]. Those at the right side of each complex definition are the different combination schemes of the water molecules.

involved systems depends on the following two factors that, (1) the scheme would produce a hydrate with poorer stability among its isomers and (2) the poorer stability has been confirmed by other ion-involved systems, in which the absent scheme has been tested. After comparing the relative energies of the dihydrates obtained by these different schemes, the most stable NO/OO1/OH-mode structures could be obtained. The same is true for the following multihydrates. Results show that the NO/OO/OH-mode dihydrates with two water molecules both bound at the metal ion are the most stable among each series of isomers. Among them, Table 1 shows that the OH-mode dihydrate has replaced the NO-mode one, becoming the lowest energy complex (see Li/Na/K–OH · 2W in Fig. 1). Because the (C_α–)H of a glycine cannot bind a water molecule,[43] no hydrates with the hydration at the (C_α–)H were obtained.

On the basis of these dihydrates, trihydrates can also be obtained by binding the third water molecule at the remaining active sites. Thus four Na–NO · 3W isomers, three Na–OO1 · 3W isomers and one Na–OH · 3W are optimized. The highest B3LYP/6-311+G*//HF/6-31G* energy of the Na–NO–3W3 (2.0 kcal mol^{-1}) among three NO-mode isomers reveals that the hydration at the amino hydrogen(s) of the NO-mode glycine is the most unfavorable for the stability of the system (see Fig. S2†). Thus the NO-mode dihydrates with two water molecules respectively bound at the metal ion end and the amino hydrogen(s) are not discussed. Due to the similarity in structures between Na–NO/OO1 and Li–NO/OO1,[25] and between Na–NO/OO1 · *n*W and Li–NO/OO1 · *n*W,[36–38,43] only two NO-mode, three OO1-mode and one OH-mode glycine–Li^+ dihydrates are displayed in Fig. S1. Relative energies reveal that the Li/Na/K–NO/OH · 3W and Li–OO1 · 3W with three water molecules binding at the metal ion are the most stable among each corresponding NO/OH/OO1-mode hydrates, while the Na/K–OO1 · 3W with two water molecules bound at the metal ion end and one at the amino hydrogen are the most stable ones among the OO1-mode trihydrates. This can be attributed partly to the fact that a lithium ion can be bound by up to four ligands.[44] These results are consistent with the conclusions of Ye *et al.*[38] and Benzakour *et al.*[36] Relative energies show that trihydration does not stabilize the OO1 mode over the NO one and the OH mode is still preferred among the three most stable different modes. For example, the energies of Li–NO/OO1 · 3W are 3.5/1.0 kcal mol^{-1}, respectively, more than that of the Li–OH · 3W. The relative energies obtained by Ye *et al.* [36] are 3.4/1.2 kcal mol^{-1}, which are in good agreement with our results.

For the tetrahydrated glycine–Na^+, five NO modes, five OO1 modes and one OH mode are designed and optimized with the HF method. Correspondingly, eleven different hydrates are obtained (see Fig. 2 and Fig. S2†). Similarly, the tetrahydrated glycine–Li^+/K^+ are also obtained. For the most stable Na–NO · 4W, HF and B3LYP optimizations give different structures, but only the B3LYP results are discussed. B3LYP-reoptimized results reveal that Li/Na/K–NO · 4W with four water molecules coordinating at the metal ion are the most stable among the isomers, and the Li/Na/K–OO1 · 4W with two water molecules coordinating at the metal ion and two at the two amino hydrogens, respectively, are the most stable ones.[38] Different from these NO/OO1-mode tetrahydrates, the differences in structure occur between the most stable Li/Na–OH · 4W and the K–OH · 4W. For the former, Fig. 1 shows that only three water molecules coordinate to the metal ion directly, and the fourth water hydrogen-bonds with both the hydroxyl oxygen of glycine and two hydrogens of neighboring water molecules. For the latter, four water molecules all coordinate at the potassium ion. These may be attributed to the larger radius of the potassium ion and its poorer electron density than the former.[44,45] Relative energies show that tetrahydration can make Li/Na/K–OO1 · 4W more stable than their corresponding Li/Na/K–NO · 4W counterparts though the OH modes are still the most stable ones among the three different modes, *i.e.*, four water molecules can make the zwitterionic glycine–Li^+/Na^+/K^+ complexes more stable than the corresponding NO-mode counterparts. For example, the energy of Li–OO1 · 4W is 0.1 kcal mol^{-1} less stable than that of Li–OH · 4W, but 2.5 kcal mol^{-1} more stable than that of Li–NO · 4W. It is expected that multihydration can make the OO1-mode hydrate more stable than the OH-mode one, or would eventually make the OH-mode complex become the OO1-mode complex because the hydration is more favorable for the OO1-mode stability.[30]

3.1.2 Structure comparisons of the most stable M–OH/NO/OO1 · *n*W complexes.

For the gas-phase glycine–Li^+/Na^+/K^+, their OH/NO/OO1-mode structures were first optimized as the reactants for the following hydration. The M–OH bond lengths should be noted in the three different ion-involved OH-mode structures. Results show that the distances are 1.032 Å (Li–OH), 1.020 Å (Na–OH) and 1.012 Å (K–OH), respectively, decreasing gradually with the decrease of charge density over the ions ($K^+ < Na^+ < Li^+$). This indicates that the hydroxyl hydrogen will transfer from the hydroxyl oxygen to the amino nitrogen when the charge density is sufficient over the ion bound by the glycine. The prediction is well confirmed by the divalent ion-involved cases since all their OH-mode structures degenerate into the OO2-mode ones (see discussion in the next section).[28]

For the monohydrate, Benzakour *et al.*[36] had showed that Li–OO1 · W1 (see Fig. S1†) was the most stable among its three different mode isomers, while our calculations reveal that NO-mode Li–NO · W is the most stable among the three different modes. Our result is consistent with that of Ye *et al.*[38] for the monohydrated glycine–Na^+ (Na–OH/NO/OO1 · W), and of Lemoff *et al.*[37] for the monohydrated valine–Li^+. The most stable OO1-mode monohydrate for glycine–Li^+/Na^+ is Li/Na–OO1 · W, in which the metal ion forms bonds with both carboxyl oxygens of the glycine and the water molecule is bound at the metal ion. The OO1-mode K–OO1 · W is the structure with the water molecule not only attached to the metal ion but also hydrogen bonding at the hydroxyl oxygen of the glycine. The most stable OH-mode structures are also different for the three systems involving different ions. Calculations show that the water in Li/Na–OH · W is only attached at the metal ion with 1.866 Å/2.217 Å Li/Na–O distances, respectively, and neither ion interacts with the hydroxyl oxygen. The water in K–OH · W, however, not only bonds with the potassium ion (2.581 Å) but also hydrogen bonds with the hydroxyl oxygen (2.014 Å) of the glycine. The gradually increased distances between the metal ion and the carboxyl oxygen in the three monohydrates involving different ions reveal that the bonding strength becomes weak along with the increase of ion radius. The results are also confirmed by the ordering of their binding energies, -44.9 kcal mol^{-1}(Li–OH · W) $>$ -34.0 kcal mol^{-1} (Na–OH · W) $>$ -27.2 kcal mol^{-1} (K–OH · W).

For the dihydrates involving the three different alkali-metal ions, they have similar OH, NO or OO1-mode structures. The same is true for their trihydrates except for the OO1-mode ones. Fig. 1 shows Li–OO1 · 3W with three water molecules attached at the lithium ion and Na/K–OO1 · 3W with two water molecules at the metal ion and one at the amino hydrogen.

The trend continues in the tetrahydrated OO1-mode structures. A relative energy comparison reveals that the most stable OO1-mode tetrahydrates of the three systems involving different metal-ions all have the structures in which two water molecules attach at the metal ion and two at two amino hydrogens. For both NO and OH modes, four water molecules all attach at the metal ion directly (K–OH/NO · 4W) or indirectly (Li/Na–OH/NO · 4W) to produce the most stable structures according to the different ion radii and charge densities over the ions. Among them, the OH-mode tetrahydrates are still the most stable, however, the further hydration at the amino hydrogen would make the OO1-mode multihydrates more stable or even the OH-mode structures become the OO1-mode ones. In other words, the hydroxyl hydrogen would transfer to the amino nitrogen because the hydration is more favorable to the OO-mode stability.[30] For example, in the most stable K–OO1 · (2,3,4)W hydrates, 0, 1 and 2 water molecules are attached at the amino hydrogen(s), respectively. Consequently, the distances between the hydroxyl oxygen and hydroxyl hydrogen, being 1.522 Å, 1.698 Å and 1.783 Å, respectively, indicate that the amino nitrogen has an increasingly more favorable proton affinity than the carboxyl oxygen. Thus multihydration would make the OH-mode hydroxyl hydrogen transfer to the amino nitrogen.

3.1.3 Hydrates of divalent alkali-earth-metal-ion chelated glycine derivatives. In the search for the most stable divalent isomers among the OH/NO/OO-mode series, the same schemes as those of the monovalent alkali-metal-ion involved systems were adopted (see Fig. 2 and S4†). Optimizations show that all initially guessed OH-mode structures degenerate into the corresponding OO2-mode ones due to the large electrostatic effect of these divalent ions.[28] Thus the following discussion focuses only on the NO/OO2-mode structures. Previous studies had shown that the ground states of all these divalent alkali-earth-metal-ion but Be^{2+} chelated glycine derivatives had the OO2-mode structures.[28,46] For the OO-mode glycine–Be^{2+}, Table 1 reveals that its energy is higher by 6.5 kcal mol^{-1} than the NO-mode one, in excellent agreement with that (6.5 kcal mol^{-1}) obtained by Strittmatter *et al.*[46] at the B3LYP/LACVP+(d,p) level. The present calculations reveal that monohydration can reduce the relative energy to 2.8 kcal mol^{-1}, while dihydration can reverse their relative stability ordering. Results show that the most stable Be–OO2 · 2W has become more stable than the Be–NO · 2W with a 5.4 kcal mol^{-1} energy difference, and the MP2 result (3.8 kcal mol^{-1}) also confirms this ordering. These imply that the multihydration favors the stability of the OO-mode glycine–Be^{2+} over that of the NO-mode one. This observation is similar to the finding in our previous study on the glycine–Zn^{+} systems.[27a]

Different from those glycine–Be^{2+} derivatives, relative energies show that the most stable OO2 modes are more stable by 7.9 and 12.3 kcal mol^{-1} than the corresponding most stable NO modes for Mg^{2+}- and Ca^{2+}-chelated glycine systems, respectively. The values obtained by Strittmatter *et al.*[46] are 6.9 and 9.2 kcal mol^{-1}, respectively, in agreement with our results. The smaller differences arise from the different computational methods employed. For the most stable glycine–Mg^{2+} monohydrates and dihydrates, the energy differences between their NO and corresponding OO2 modes are 6.8 and 5.9 kcal mol^{-1}, respectively, decreased somewhat relative to their non-hydrated counterparts. This is because multihydration reduces the electrostatic interaction between the metal ion and the glycine ligand in the OO2 mode more than in the NO mode.[46] Similar phenomena have also been observed for the Ca^{2+}-involved systems. Calculated relative energies between their most stable NO modes and the corresponding OO2 counterparts of the monohydrates and dihydrates are 10.5 and 9.0 kcal mol^{-1}, respectively. The higher relative energies indicate that multihydration would also keep the OO2-mode structures more stable than the NO-mode ones for these divalent metal-ion involved glycine systems. This has also been implied by the suggestion of Rode that compounds vital to the early life forms on primordial earth may have been formed through an OO-mode mechanism involving Cu^{2+}.[47]

3.2 Binding energies of the most stable modes

For the most stable NO, OO, and OH-mode glycine–M^{+} and glycine–M^{2+} hydrates, their metal ion–ligand binding energies are listed in Tables 2 and 3, respectively. The values in the two tables show that the MP2-results are smaller than the corresponding B3LYP-counterparts. The observations are consistent with the reports of Moision and Armentrout.[48] For example, the B3LYP-binding energies of Li–NO, Na–NO and K–OH are −61.3, −42.0 and −29.0 kcal mol^{-1}, respectively, higher than their MP2 counterparts (−56.7, −36.9 and −28.4 kcal mol^{-1} respectively) and other theoretical results;[25,34c] similarly for the Be^{2+}/Mg^{2+}/Ca^{2+}-involved glycine derivatives (see Table 3). However, both levels give similar ordering. Thus the binding energies obtained for the hydrates at the two levels should also be reliable although there are no experimental or theoretical values with which to compare.

For these hydrates, we can observe that the binding strengths decrease with an increase in the number of water molecules, except for Na/K–OO1 · 3W and Li/Na/K–OO1 · 4W. This observation can be explained from the optimized structures in Fig. 1. Results show that in both of the two most stable OO1-mode trihydrates one water molecule is attached to an amino hydrogen instead of all being attached to the metal ion, while in the OO1-mode tetrahydrates two water molecules are attached to two amino hydrogens, respectively. It is known that the interaction between the metal ion and the glycine mainly derives from the electrostatic contribution. Hydration at the metal ion would cause electron delocalization from water to the metal ion to reduce the interaction,[38] as evidenced by the

Table 2 Binding energies (kcal mol^{-1}) of M–OH/NO/OO1 · nW (M = Li, Na, or K, and n = 0–4) (entries 1–15) obtained at (**I**) B3LYP/6-311+G(2d,2p)//B3LYP/6-31G(d,p) and (**II**) MP2/6-311+G(2d,2p)//B3LYP/6-31G(d,p) levels including BSSEs

Entry	Complex	**I** (kcal mol^{-1})	**II** (kcal mol^{-1})
1	Li–OH/NO/OO1	−50.6/−61.3/−55.6	−47.0/−56.7/−52.2; —/[−56.4^a, −58.3^b]/—
2	Na–OH/NO/OO1	−38.1/−42.0/−38.9	−33.7/−36.9/−34.5; —/[−37.8^a, −39.1^b]/—
3	K–OH/NO/OO1	−29.0/−29.4/−26.7	−28.4/−28.6/−26.3; −27.4^a/—/—
4	Li–OH/NO/OO1 · W	−44.9/−50.5/−44.2	−41.6/−47.6/−42.2
5	Na–OH/NO/OO1 · W	−34.0/−36.4/−34.4	−30.2/−29.0/−28.1
6	K–OH/NO/OO1 · W	−27.2/−25.4/−24.1	−26.8/−25.1/−23.7
7	Li–OH/NO/OO1 · 2W	−35.5/−36.2/−29.5	−34.4/−35.8/−29.5
8	Na–OH/NO/OO1 · 2W	−29.2/−28.6/−26.4	−27.0/−26.7/−23.7
9	K–OH/NO/OO1 · 2W	−24.2/−21.6/−20.1	−24.2/−21.8/−19.9
10	Li–OH/NO/OO1 · 3W	−26.3/−25.8/−23.1	−26.5/−25.6/−23.4
11	Na–OH/NO/OO1 · 3W	−24.5/−23.9/−35.4	−21.1/−21.3/−30.8
12	K–OH/NO/OO1 · 3W	−21.3/−20.8/−28.8	−21.5/−20.9/−26.8
13	Li–OH/NO/OO1 · 4W	−21.9/−20.8/−52.5	−22.8/−20.5/−51.3
14	Na–OH/NO/OO1 · 4W	−20.9/−20.1/−44.1	−19.1/−18.8/−41.2
15	K–OH/NO/OO1 · 4W	−19.2/−20.6/−37.4	−20.0/−20.9/−37.0

[a] From ref. 25 obtained at the MP2/6-31G* level. [b] From ref. 34*c* obtained at the MP2/6-311++G** level.

Table 3 Binding energies (kcal mol^{-1}) of M–NO/OO2 $\cdot$ nW (M = Be, Mg, Ca, and n = 0–2) (entries 1–9) obtained at (**I**) B3LYP/6-311+G(2d,2p)//B3LYP/6-31G(d,p) and (**II**) MP2/6-311+G(2d,2p)//B3LYP/6-31G(d,p) levels including BSSEs

Entry	Complex	**I** (kcal mol^{-1})	**II** (kcal mol^{-1})
1	Be–NO/OO2	−282.9/−275.5	−268.8/−263.5; −280.2[a]/[−297.0[a], −274.6[b]]
2	Mg–NO/OO2	−163.4/−170.7	−151.8/−161.2; −160.9[a]/[−191.8[a], −170.3[b]]
3	Ca–NO/OO2	−113.2/−125.2	−105.2/−118.1; —/−111.8[b]
4	Be–NO/OO2 $\cdot$ W	−217.4/−213.2	−210.6/−208.0
5	Mg–NO/OO2 $\cdot$ W	−139.7/−145.9	−132.0/−140.0
6	Ca–NO/OO2 $\cdot$ W	−96.6/−106.7	−92.0/−103.1
7	Be–NO/OO2 $\cdot$ 2W	−140.2/−145.3	−139.3/−143.2
8	Mg–NO/OO2 $\cdot$ 2W	−110.5/−116.0	−106.9/−113.7
9	Ca–NO/OO2 $\cdot$ 2W	−84.1/−92.7	−81.2/−90.6

[a] From ref. 46 obtained at B3LYP/LACVP+(d,p) level. [b] From ref. 28 obtained at B3LYP/6-311+G*//B3LYP/6-31G* level.

increase of M–O distances and the decrease of charge over these metal ions. For example, the Na–O distances are from 2.290/2.247 (Na–NO/OH $\cdot$ 2W), 2.292/2.296 (Na–NO/OH $\cdot$ 3W) to 2.307/2.208 Å (Na–NO/OH $\cdot$ 4W), an increasing trend. The charges over each Na$^+$ are 0.9/0.92 (Na–NO/OH $\cdot$ 2W), 0.9/0.9 (Na–NO/OH $\cdot$ 3W), and 0.89/0.89 (Na–NO/OH $\cdot$ 4W), a decreasing trend. However, hydration at the amino hydrogens would cause electron delocalization from water to the glycine moiety to increase the interaction. For example, the OO1-mode structures (Na–OO1 $\cdot$ 2,3,4W) are produced by the attachment of zero, one to two water molecules at the amino hydrogen(s) of the Na–OO1 $\cdot$ 2W. Their Na–O distances are 2.233, 2.218 and 2.208 Å, respectively, a decreasing trend. The charges over Na$^+$ in the three OO1-mode hydrates are 0.92, 0.91 and 0.91, almost a constant. The same is true for the three K$^+$-involved counterparts (0.95, 0.95 and 0.95). The charges over Li$^+$ in the three Li$^+$-involved counterparts are 0.87, 0.82 and 0.86, a first-decreasing-then-increasing trend because three water molecules are attached at Li$^+$ in Li–OO1 $\cdot$ 3W, while only two are attached at the metal ion and another two are at the amino hydrogens in Li–OO1 $\cdot$ 4W. The decreasing M–O distances and almost constant, or even increasing, ionic charges also indicate the probable increase of the binding strength for these OO1-mode hydrates. Thus the ordering of binding energies, Na/K–OO1 $\cdot$ 4W > Na/K–OO1 $\cdot$ 3W > Na/K–OO1 $\cdot$ 2W, has been observed. According to the trend, Na–OO1 $\cdot$ 2W2 (see Fig. S2†) formed by attaching two water molecules, respectively, to the metal ion and an amino hydrogen of the Na–OO1 should also have larger binding strength. Relative energies show, however, that the structure is a higher energy one among the three considered OO1-mode isomers, thus it is not considered in Fig. 1.

Excluding these OO1-mode structures, the binding-strength ordering of the others is in good agreement with their relative stability ordering. For example, the binding-energy ordering for dihydrated glycine–Na$^+$ complexes is Na–OH $\cdot$ 2W (−29.2 kcal mol^{-1}) > Na–NO $\cdot$ 2W (−28.6 kcal mol^{-1}) > Na–OO1 $\cdot$ 2W (−26.4 kcal mol^{-1}), while their relative energies are 0.0, 0.5 and 1.5 kcal mol^{-1}, respectively. Thus the larger the binding strength is, the more stable the structure would be. For the three different alkali metal ions, the binding-strength ordering, glycine–Li$^+$ $\cdot$ nW > glycine–Na$^+$ $\cdot$ nW > glycine–K$^+$ $\cdot$ nW, is observed. For example, the binding energies of Li/Na/K–OH $\cdot$ W are −44.9, −34.0 and −27.2 kcal mol^{-1}, respectively, a decreasing trend. The change in structure and binding strength with hydration number can be observed by comparing the M–O distances in the corresponding hydrates. Taking the most stable OH-mode glycine–K$^+$ hydrates as examples, the K–O (carboxyl oxygen) distances in K–OH $\cdot$ W, K–OH $\cdot$ 2W, K–OH $\cdot$ 3W, K–OH $\cdot$ 4W are 2.602 Å, 2.642 Å, 2.679 Å and 2.715 Å, respectively. Correspondingly, the binding energies are −27.2, −24.2, −21.3 and −19.2 kcal mol^{-1}. Thus the increase of the hydration number at the metal ion site can weaken the binding strength between the metal ion and the glycine ligand and elongate bond distance.

For all the divalent alkali-earth-metal cationized glycine derivatives except the Be^{2+} derivative, the OO2 modes are more stable than the corresponding NO modes,[28,46] as observed for the divalent transition-metal-ion chelated systems.[26,27,34] Our calculations show that the stepwise hydration cannot change the relative stability of the two different modes. In other words, the glycine derivatives bound by some alkali-earth-metal ions still prefer the OO2 mode to the NO one in aqueous solution, just as the free glycine ligands do. The larger binding strengths of the OO2-mode hydrates over their corresponding NO-counterparts listed in Table 3 also reflect the point well. Our results are also in agreement with other available theoretical results,[28,46] and the minor errors derive from the different calculation methods and basis sets used.

Having the smallest ion radius among its main group ions, Be^{2+} takes on some particularity when it interacts with glycine conformers, *i.e.*, its OO2-mode structure is less stable than the NO-mode one.[46] Only dihydration can change the relative stability, confirmed by their binding energy strengths. Both B3LYP and MP2 levels indicate that Be–OO2 $\cdot$ 2W has a higher binding strength (−145.3/−143.2 kcal mol^{-1}) than its corresponding NO-mode dihydrate (−140.2/−139.3 kcal mol^{-1}), *i.e.*, both levels show that Be–OO2 $\cdot$ 2W has become the global minimum among the isomers. Thus the binding energy ordering is also completely consistent with the structural stability. Now 0.33/0.32 charge is transferred from the Be atom in Be–NO/OO2 $\cdot$ 2W to the ambient attached water and glycine ligands. Thereinto, the charge transfer to the water molecules is 0.09/0.08, obtained by comparison with that of the ion in Be–NO/OO2. The 0.01 charge difference for the two modes (Be–NO $\cdot$ 2W and Be–OO2 $\cdot$ 2W) indicates that the hydration would be more favorable to the OO2-mode binding. Similar phenomena have also been observed in the Mg/Ca-ion involved systems, but the charge transfers of the two ions to the ambient ligands are less than those of the Be ion in the same mode hydrates (see Table S1†).

4. Conclusions

The number of water molecules needed to stabilize the glycine–M$^+$/M$'^{2+}$ (M = Li, Na, K and M$'$ = Be, Mg, Ca) isomers has been discussed at both the B3LYP/6-311+G(2d,2p)//B3LYP/6-31G(d,p) and MP2/6-311+G(2d,2p)//B3LYP/6-31G(d,p) levels in the present paper. The results show that the OO-mode glycine–Li$^+$/Na$^+$/K$^+$/Be^{2+} complexes can become more stable than the NO-mode ones in aqueous solution though the global minima of glycine–Li$^+$/Na$^+$/Be^{2+} and glycine–K$^+$ in the gas phase are the NO-mode structures and OH-mode one, respectively.[25–29,35,38] In detail, four water molecules can make the most stable OO1-mode glycine–Li$^+$/Na$^+$/K$^+$ hydrates more stable than their corresponding NO-mode counterparts, while the number of water molecules needed to make the OO2-mode glycine–Be^{2+} complex more stable than the NO-mode one is two. For the gas-phase and monohydrated glycine–Li$^+$/Na$^+$

View Article Online

isomers, the NO mode is the most stable among their three different-mode structures.[25–29,35,36,38] The (di–tetra)hydrates, however, prefer the OH mode to the other two. The OH-mode structure is always the most stable among the three different OH/NO/OO1-mode isomers for the gas-phase and for the (mono–tetra)hydrated glycine–K^+ complexes.[36,38] Both theoretical and experimental results confirm that the ground-state glycine–Mg^{2+}/Ca^{2+} derivatives prefer the OO2 modes to the NO ones both in the gas phase and in aqueous solution.[27–29,35] Therefore further hydration would not change their relative stability.

With the same coordination mode and hydration number, the binding-strength ordering, glycine–$Li \cdot nW >$ glycine–$Na^+ \cdot nW >$ glycine–$K^+ \cdot nW$, is observed due to the gradual increasing of the ion radii ($Li^+ < Na^+ < K^+$) and the corresponding decreasing of the charge distribution over these ions.[44,45] The ordering of binding energies is well consistent with that of the relative energies for most of the three different modes, *i.e.*, the larger the binding strength is, the more stable the corresponding structure would be.

The cases of the Na/K–OO1 $\cdot$ 3W and the Li/Na/K–OO1 $\cdot$ 4W hydrates are in disagreement with the above ordering due to the change of attachment site of the third and fourth water molecules in these structures. In detail, the attachments of the third and fourth water molecules at the amino hydrogen(s) instead of at the metal ion in these OO1-mode (tri–tetra) hydrates are more favorable to the M–ligand binding. Moreover, the trend rises gradually along with the number increase of the attached water molecules, for example Na–OO1 $\cdot$ 2W (-26.4 kcal mol^{-1}) < Na–OO1 $\cdot$ 3W (-35.4 kcal mol^{-1}) < Na–OO1 $\cdot$ 4W (-44.1 kcal mol^{-1}). Further hydration at the amino hydrogen(s) is expected to make the most stable OH-mode structure less stable than the most stable OO1-mode one or even transform the OH-mode structure into the OO1-mode one because the hydration is more favorable to the OO-mode stability,[30,38] evidenced by the changes of both the M–O distances and ionic charges.

Acknowledgements

This work was supported by NSFC (20273040, 29973022), Foundations for doctoral start-up by Jinan University (B0418), NCET and the Natural Science Foundation of Shandong Province (Z2003B01). Support from SRFDP and SCF for ROCS, SEM is also acknowledged. Some of the calculations were performed at the Virtual Laboratory of Computational Chemistry, CNIC, CAS and the High-performance Computational Center of Shandong University, respectively.

References

1 A. Fersht, *Enzyme Structure and Mechanism*, W. H. Freeman, New York, 1985.
2 V. N. Balaji and K. Ramnarayan, in *Biologically Active Peptides: Design, Synthesis and Utilization*, ed. W. V. Williams and D. B. Weiner, Technomic Publishing, Basel, Switzerland, 1991.
3 D. Yu, D. A. Armstrong and A. Rauk, *Can. J. Chem.*, 1992, **70**, 1762.
4 K. Zhang and A. Chung-Phillips, *J. Phys. Chem. A*, 1998, **102**, 3625.
5 M. Ramek, V. K. W. Cheng, R. F. Frey, S. Q. Newton and L. Schafer, *J. Mol. Struct.*, 1991, **186**, 12, and references therein.
6 J. H. Jensen and M. S. Gordon, *J. Am. Chem. Soc.*, 1991, **113**, 7917.
7 A. G. Császár, *J. Am. Chem. Soc.*, 1992, **114**, 9568.
8 R. F. Frey, J. Conffin, S. Q. Newton, M. Ramek, V. K. W. Chang, F. A. Momany and L. Schafer, *J. Am. Chem. Soc.*, 1992, **114**, 5369.
9 C. Chipot, B. Maigret and L.-L. Rivail, *J. Phys. Chem.*, 1992, **96**, 10276.
10 A. Vijay and D. N. Sathyanarayana, *J. Phys. Chem.*, 1992, **96**, 10735.
11 A. A. Bliznyuk, H. F. Schaefer III and I. J. Amster, *J. Am. Chem. Soc.*, 1993, **115**, 5149.
12 C.-H. Hu, M. Shen and H. F. Schaefer III, *J. Am. Chem. Soc.*, 1993, **115**, 2923.
13 V. Barone, C. Adamo and F. Lelj, *J. Chem. Phys.*, 1995, **102**, 364.
14 (*a*) I. D. Reva, A. M. Plokhotnichenko, S. G. Stepanian, A. Y. Ivanov, E. D. Radchenko, G. G. Sheina and Y. P. Blagoi, *Chem. Phys. Lett.*, 1995, **232**, 141; (*b*) I. D. Reva, A. M. Plokhotnichenko, S. G. Stepanian, A. Y. Ivanov, E. D. Radchenko, G. G. Sheina and Y. P. Blagoi, *Chem. Phys. Lett.*, 1995, **235**, 617.
15 A. G. Császár, *J. Mol. Struct.*, 1995, **346**, 141.
16 (*a*) P. D. Godfrey and R. D. Brown, *J. Am. Chem. Soc.*, 1995, **117**, 2019; (*b*) P. D. Godfrey, R. D. Brown and F. M. Rodgers, *J. Mol. Struct.*, 1996, **376**, 65.
17 J. J. Neville, Y. Zheng and C. E. Brion, *J. Am. Chem. Soc.*, 1996, **118**, 10533.
18 M. Ramek, F. A. Momany, D. M. Miller and L. Schafer, *J. Mol. Struct.*, 1996, **375**, 189.
19 R. D. Sueram and F. J. Lovas, *J. Mol. Spectrosc.*, 1980, **72**, 372.
20 M. J. Locke and R. T. McIver, *J. Am. Chem. Soc.*, 1983, **105**, 4226.
21 M. S. Gordon and J. H. Jensen, *Acc. Chem. Res.*, 1996, **29**, 536.
22 P. I. Nagy and B. Noszal, *J. Phys. Chem. A*, 2000, **104**, 6834.
23 M. Ramek and P. I. Nagy, *J. Phys. Chem. A*, 2000, **104**, 6844.
24 F. Jensen, *J. Am. Chem. Soc.*, 1992, **114**, 9533.
25 S. Hoyau and G. Ohanessian, *Chem.–Eur. J.*, 1998, **8**, 1561.
26 F. Rogalewicz, G. Ohanessian and N. Gresh, *J. Comput. Chem.*, 2000, **21**, 963.
27 (*a*) H. Ai, Y. Bu and K. Han, *J. Chem. Phys.*, 2003, **118**, 10973; (*b*) H. Ai and Y. Bu, *J. Chem. Phys.*, 2004, **120**, 2208.
28 H. Ai, Y. Bu and P. Li, *Int. J. Quantum Chem.*, 2003, **94**, 205.
29 K. Zhang, D. M. Zimmerman, A. Chung-Phillips and C. J. Cassady, *J. Am. Chem. Soc.*, 1993, **115**, 10812.
30 J. H. Jensen and M. S. Gordon, *J. Am. Chem. Soc.*, 1995, **117**, 8159.
31 M. Remko and B. M. Rode, *Chem. Phys. Lett.*, 2000, **316**, 489.
32 (*a*) K. O. Håkansson and P. L. Jorgensen, *Ann. N. Y. Acad. Sci.*, 2003, **986**, 163; (*b*) P. L. Jorgensen, *Ann. N. Y. Acad. Sci.*, 2003, **986**, 22.
33 (*a*) C. Toyoshima and H. Nomura, *Nature*, 2002, **418**, 605; (*b*) W. P. Jencks, T. Yang, D. Peisach and J. Myung, *Biochemistry*, 1993, **32**, 7030.
34 (*a*) J. Bertan, L. Rodriguez-Santiago and M. Sodupe, *J. Phys. Chem. B*, 1999, **103**, 2310; (*b*) S. Hoyau and G. Ohanessian, *J. Am. Chem. Soc.*, 1997, **119**, 2016; (*c*) T. Marino, N. Russo and M. Toscano, *J. Inorg. Biochem.*, 2000, **79**, 179; (*d*) L. Rodriguez-Santiago, M. Sodupe and J. Tortajada, *J. Phys. Chem. A*, 2001, **105**, 5340; (*e*) T. Shoeib, C. F. Rodriquez, M. Siu and A. C. Hopkinson, *Phys. Chem. Chem. Phys.*, 2001, **3**, 853.
35 S. Hoyau, J.-P. Pélicier, F. Rogalewicz, Y. Hoppilliard and G. Ohanessian, *Eur. J. Mass. Spectrom.*, 2001, **7**, 303.
36 M. Benzakour, A. Cartier, M. Mcharfi and A. Daoudi, *J. Mol. Struct. (THEOCHEM)*., 2004, **681**, 99.
37 A. S. Lemoff and E. R. Williams, *J. Am. Soc. Mass Spectrom.*, 2004, **15**, 1014.
38 S. J. Ye, R. M. Miosion and P. B. Armentrout, *Int. J. Mass Spectrom.*, 2005, **240**, 233.
39 (*a*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (*b*) A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098; (*c*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, **37**, 785; (*d*) S. H. Vosko, L. Wilk and M. Nusair, *Can. J. Phys.*, 1980, **58**, 1200.
40 (*a*) C. Moller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618; (*b*) M. Head-Gordon, J. A. Pople and M. J. Frisch, *Chem. Phys. Lett.*, 1988, **153**, 503.
41 S. F. Boys and F. Bermardi, *Mol. Phys.*, 1970, **19**, 553.
42 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, *GAUSSIAN 98 (Revision A.9)*, Gaussian, Inc., Pittsburgh, PA, 1998.
43 H. Ai and Y. Bu, *J. Phys. Chem. B*, 2004, **108**, 1241–1254.
44 K. Hashimoto and T. Kamimoto, *J. Am. Chem. Soc.*, 1998, **120**, 3560.
45 A. Wakisaka and Y. Watanabe, *J. Phys. Chem. B*, 2002, **106**, 899.
46 E. F. Strittmatter, A. S. Lemoff and E. R. Williams, *J. Phys. Chem. A*, 2000, **104**, 9793.
47 B. M. Rode, *Peptides (N. Y.)*, 1999, **20**, 773.
48 R. M. Moision and P. B. Armentrout, *J. Phys. Chem. A*, 2002, **106**, 10350.