

## Research Article

# Theoretical Study on Cyclopeptides as the Nanocarriers for $\text{Li}^+$ , $\text{Na}^+$ , $\text{K}^+$ and $\text{F}^-$ , $\text{Cl}^-$ , $\text{Br}^-$

Lili Liu<sup>1</sup> and Shimou Chen<sup>2</sup>

<sup>1</sup> Department of Chemistry, School of Science, Beijing Technology and Business University, Beijing 100048, China

<sup>2</sup> Key Laboratory of Green Process and Engineering, Institute of Process Engineering (IPE), Chinese Academy of Sciences (CAS), Beijing 100190, China

Correspondence should be addressed to Shimou Chen; [chenshimou@ipe.ac.cn](mailto:chenshimou@ipe.ac.cn)

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The interaction process between a series of cyclopeptide compounds  $\text{cyclo}(\text{Gly})_n$  ( $n = 4, 6, 8$ ) and monovalent ions ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{F}^-$ ,  $\text{Cl}^-$ , and  $\text{Br}^-$ ) was studied using theoretical calculation. The mechanism of combination between the  $\text{cyclo}(\text{Gly})_n$  and ions was discussed through binding energy, Mulliken electron population, and hydrogen bond. It was found that for the same cyclopeptide the binding energy has the order of  $\text{cyclo}(\text{Gly})_n\text{-Li}^+ > \text{cyclo}(\text{Gly})_n\text{-Na}^+ > \text{cyclo}(\text{Gly})_n\text{-K}^+$  and  $\text{cyclo}(\text{Gly})_n\text{-F}^- > \text{cyclo}(\text{Gly})_n\text{-Br}^- > \text{cyclo}(\text{Gly})_n\text{-Cl}^-$ . The binding energy manifests the stable complex of  $\text{cyclo}(\text{Gly})_n$  and ions can be formed, and the different energy shows the potential use of  $\text{cyclo}(\text{Gly})_n$  as nanocarriers for metal ions or the extractant for ions separation.

## 1. Introduction

As an important family of host-guest complexation, ion carriers play an important role in various biological processes [1]. In particular, in biomedical research, the controlled delivery of drugs to specific tissues in the body is an ongoing challenge. Ion carriers are promising delivery vehicles that offer increased drugs circulation times and enhanced dissolution rates and bioavailability. Macrocyclic compound is one of the best choices as ion carriers because of its special structure. For example, crown ether [2, 3], cyclopeptide [4–9], and calixarene [10–12] can combine with alkali metal ions or alkaline-earth metal ions to form a dissolvable complex or act as ion and neutral molecular carriers. Since the 1940s, when the first cyclopeptide gramicidin was found [13], due to its similar structure to macrocyclic compound, the cyclopeptide aroused much interest in host-guest chemistry. It is demonstrated that cyclopeptides are promising materials as carriers, antibiotics, regulators of membrane ion and systems for specific guest recognition, and so forth [5, 14]. Many theoretical calculations on cyclopeptides-ions complex were performed in order to direct the construction of ion-assisted cyclopeptide system [15–17]. Owing to the metabolism

stability and the high bioavailability, many of them could be used as prodrugs, medicament, and ion carriers [18, 19]. It is believed that the biological activities of cyclopeptide with metal ion are of much potential application in medical and biological chemistry.

In all subjects related to cyclopeptide or modified cyclopeptide as ion carriers, the stereoselectivity on ions becomes the focus of the experimental and theoretical studies. This selectivity is due to the special structure of the cyclopeptide. Cyclopeptide has a cavity structure with restricted carbonyl group and amino group on inner side of the molecule and a rigid molecule skeleton that can support the molecule cavity. Tan et al. [20] have studied the cyclopeptide composed of  $\text{cyclo}[(\text{-}\beta^3\text{-Hgly})_4\text{-}]$  through computational method. Huang et al. [21] have designed and synthesized a cystine-bearing pseudo-cyclopeptide as amphireceptor; it binds to cations or anions through the carbonyl or amino groups, respectively. Using ab initio calculations, Kim and coworkers [22] proposed that cyclic peptides may be able to serve as good amphi-ionophores because of the availability of both amide and crown-like structures within the molecule. However, to design useful cyclopeptide carrier and shed light on the related organic synthesis, various factors such as the

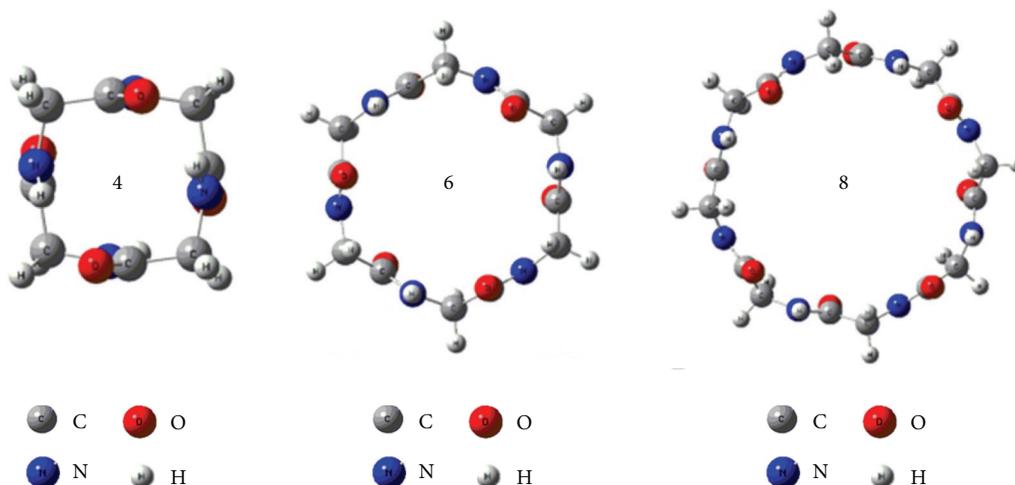


FIGURE 1: The most stable conformation of cyclo(Gly)<sub>n</sub> ( $n = 4, 6, \text{ and } 8$ ).

structure of the component peptide, peptide number, and the interaction of the ions and peptide should be studied carefully.

In the previous work reported by Zhu et al. [23], the preferred conformations of cyclic dipeptides were first studied using the density functional theory (DFT). Herein, we take a systemically theoretical study on the conformation and complexation of cyclo(Gly)<sub>n</sub> ( $n = 4, 6, \text{ and } 8$ ) and monovalent ions ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{F}^-$ ,  $\text{Cl}^-$ , and  $\text{Br}^-$ ) using the DFT B3LYP method at 6-31G(d) level. To the best of our knowledge, the study of interaction of the cycloquadpeptide, cyclohexapeptide, and cyclooctopeptide with both anions and cations synchronously would be the first report in the literature. It should be mentioned that only the cases of one cyclopeptide carrying one ion were discussed in this paper; that is, the ratio of the cyclopeptide carrier to the ions receptor is 1:1. The cyclopeptide carrying multi-ions will be reported in the future.

## 2. Computational Methods

Glycine (Gly) was chosen as monomer to form cyclopeptide because of its simple structure. We begin our research with the construction of cyclohexapeptide; there are 8 different isomerides of Gly cyclohexapeptide: all of them were optimized by HF/STO-3G method and the most stable ones were selected as ion carrier for further study. Based on the stable configuration of three kinds of cyclopeptide, the complexes of three kinds of cyclopeptide with cations  $\text{K}^+$ ,  $\text{Li}^+$ , and  $\text{Na}^+$  and anions  $\text{F}^-$ ,  $\text{Cl}^-$ , and  $\text{Br}^-$  were optimized at B3LYP/6-31G level, respectively. All computations were carried out using the Gaussian 03 package [24].

## 3. Results and Discussion

**3.1. The Optimum Conformations.** The conformations of the most stable cyclohexapeptide are shown in Figure 1; all of them were optimized by HF/STO-3G method. It has a

transfiguration structure. In order to obtain a deep understanding of the characteristic of the cycloquadpeptide, cyclohexapeptide, and cyclooctopeptide, the three cyclopeptides were further optimized at B3LYP/6-31G level to guarantee that the configuration is the most stable one [25, 26].

The optimum conformations of the cation-cyclopeptide complexes were shown in Figure 2. Both the top view and side view were given considering the complicated geometry of  $\{\text{cyclo}(\text{Gly})_n - \text{M}^+\}$  ( $n = 4, 6, 8; \text{M} = \text{Li}, \text{Na}, \text{K}$ ).

From Figure 2, the  $\{\text{cyclo}(\text{Gly})_4\}$  complexes hold a  $\text{C}_1$ : the symmetry group after combining a cation to form  $\{\text{cyclo}(\text{Gly})_4 - \text{M}^+\}$  ( $\text{M} = \text{Li}, \text{Na}, \text{K}$ ) complexes. All three cations hover outside the cyclopeptide for the small space of the cycloquadpeptide cavity (as shown in Figure 2). The two carbonyl groups of the cycloquadpeptide turn towards the cation ion from original position. The configuration of cyclopeptide was distorted to a boat form, and the ions lay over the boat. The average distance between the cation ion and the carbonyl oxygen is 0.186 nm, 0.222 nm, and 0.285 nm for  $\text{Li}^+$ ,  $\text{Na}^+$ , and  $\text{K}^+$ , respectively.

Comparing the  $\{\text{cyclo}(\text{Gly})_6\}$  with  $\{\text{cyclo}(\text{Gly})_6 - \text{M}^+\}$  ( $\text{M} = \text{Li}, \text{Na}, \text{K}$ ), it can be found that all those complexes keep  $\text{C}_1$  symmetry group, and the three cation ions stay in the center of cyclohexapeptide cavity. All the six carbonyl groups on the peptide turn towards the cation. The distance between the cation and the carbonyl oxygen is 0.221 nm, 0.236 nm, and 0.267 nm for  $\text{Li}^+$ ,  $\text{Na}^+$ , and  $\text{K}^+$ , respectively.

As for cyclooctopeptide complexes, the conformation changes greatly after forming  $\{\text{cyclo}(\text{Gly})_8 - \text{M}^+\}$  ( $\text{M} = \text{Li}, \text{Na}, \text{K}$ ). The  $\{\text{cyclo}(\text{Gly})_8\}$  in Figure 1 is  $\text{C}_4$  symmetry group, and symmetry of  $\{\text{cyclo}(\text{Gly})_8 - \text{M}^+\}$  ( $\text{M} = \text{Li}, \text{Na}, \text{K}$ ) in Figure 2 degenerates to  $\text{C}_1$ . The cation was packaged up completely by the cyclooctopeptide because of the larger cavity of the cyclopeptide, and four carbonyl groups turn towards the cation. The average distance between the cation and the carbonyl oxygen is 0.193 nm, 0.241 nm, and 0.280 nm for  $\text{Li}^+$ ,  $\text{Na}^+$ , and  $\text{K}^+$ , respectively.

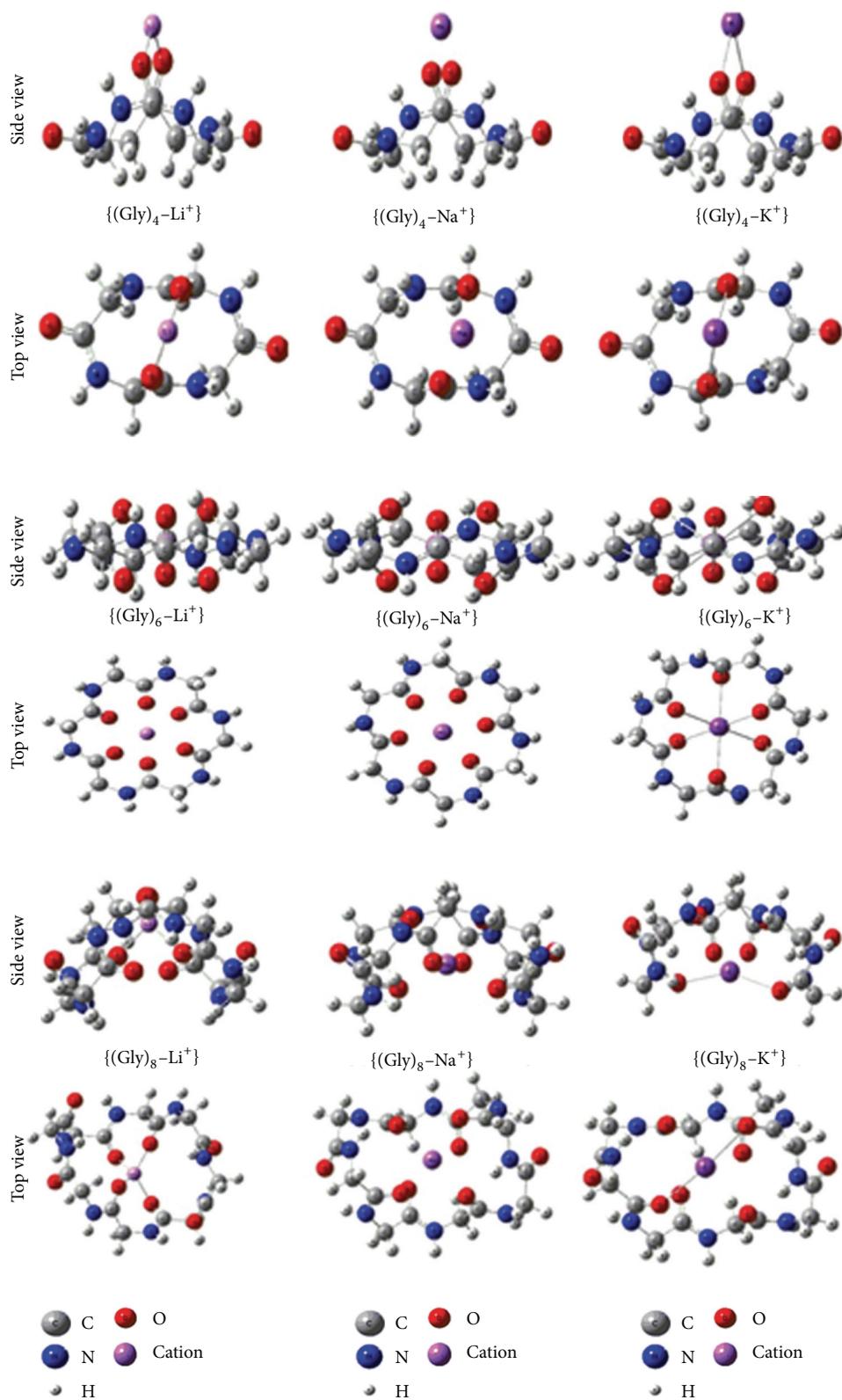


FIGURE 2: The conformation of cyclopeptide with  $Li^+$ ,  $Na^+$ , and  $K^+$  after optimization. Every structure was shown from side view and top view.

TABLE 1: The bond length (nm) and binding energy ( $\text{kJ}\cdot\text{mol}^{-1}$ ) of  $\{\text{cyclo}(\text{Gly})_n-\text{M}^+\}$ .

Complex	$\text{M}^+-\text{O}/\text{nm}$	Binding energy/ $\text{kJ}\cdot\text{mol}^{-1}$
$\{\text{cyclo}(\text{Gly})_4-\text{Li}^+\}$	0.186	207.123
$\{\text{cyclo}(\text{Gly})_4-\text{Na}^+\}$	0.222	118.326
$\{\text{cyclo}(\text{Gly})_4-\text{K}^+\}$	0.265	44.523
$\{\text{cyclo}(\text{Gly})_6-\text{Li}^+\}$	0.221	490.967
$\{\text{cyclo}(\text{Gly})_6-\text{Na}^+\}$	0.236	399.866
$\{\text{cyclo}(\text{Gly})_6-\text{K}^+\}$	0.267	241.546
$\{\text{cyclo}(\text{Gly})_8-\text{Li}^+\}$	0.193	548.325
$\{\text{cyclo}(\text{Gly})_8-\text{Na}^+\}$	0.241	415.457
$\{\text{cyclo}(\text{Gly})_8-\text{K}^+\}$	0.280	324.474

The optimized structures of  $\{\text{cyclo}(\text{Gly})_n-\text{X}^-\}$  ( $n = 4, 6, 8$ ;  $\text{X} = \text{F}, \text{Br}, \text{Cl}$ ) were shown in Figure 3. Each complex has  $\text{X}^- \cdots \text{H}-\text{N}$  hydrogen bonds, and all hydrogen atoms on the amino group turn towards the anion in  $\{\text{cyclo}(\text{Gly})_n-\text{X}^-\}$  ( $n = 4, 6$ ;  $\text{X} = \text{F}, \text{Br}, \text{Cl}$ ). The complex  $\{\text{cyclo}(\text{Gly})_4-\text{X}^-\}$  ( $\text{X} = \text{F}, \text{Br}, \text{Cl}$ ) has  $\text{C}_1$  symmetry group like the original cycloquadpeptide. Symmetry group of  $\{\text{cyclo}(\text{Gly})_6-\text{X}^-\}$  ( $\text{X} = \text{Br}, \text{Cl}$ ) is  $\text{C}_6$ , but, for the  $\{\text{cyclo}(\text{Gly})_6-\text{X}^-\}$  ( $\text{X} = \text{F}$ ) complex, the symmetry group is  $\text{C}_3$  after complexation. The symmetry group of the cyclooctopeptide degenerate from  $\text{C}_4$  to  $\text{C}_1$  after forming the complex  $\{\text{cyclo}(\text{Gly})_8-\text{X}^-\}$  ( $\text{X} = \text{F}, \text{Br}, \text{Cl}$ ).

**3.2. Binding Energy and the Distance of the Ion and Cyclopeptide Analysis.** Binding energy is a vital standard in evaluating the stability of the complex compound. Table 1 shows the energy and the distance between the cation and the carbonyl oxygen on the cyclopeptide. From the analysis of the data, for the same cyclopeptide, the average distance between cation and the carbonyl oxygen is in the order of  $\text{K}^+ > \text{Na}^+ > \text{Li}^+$ ; however, the binding energy has the order of  $\text{Li}^+ > \text{Na}^+ > \text{K}^+$  (see Figure 4). It means that the distance between the cation and the cyclopeptide is smaller; the binding energy of the compound is larger. On the other hand, for the same cation in the different cyclopeptide, the binding energy reduced in order of  $\{\text{cyclo}(\text{Gly})_8-\text{M}^+\} > \{\text{cyclo}(\text{Gly})_6-\text{M}^+\} > \{\text{cyclo}(\text{Gly})_4-\text{M}^+\}$ .

Table 2 shows the energies and the distances between the anions and H atoms on the amino groups. The results indicated that, for the same cyclopeptide, the average distance between anion and the amino hydrogen reduced in order of  $\text{Br}^- > \text{Cl}^- > \text{F}^-$ , and the binding energy increased in the order of  $\text{Cl}^- < \text{Br}^- < \text{F}^-$  (Figure 6). For the same anion in the different cyclopeptide, the binding energy reduced in order of  $\{\text{cyclo}(\text{Gly})_8-\text{X}^-\} > \{\text{cyclo}(\text{Gly})_6-\text{X}^-\} > \{\text{cyclo}(\text{Gly})_4-\text{X}^-\}$  ( $\text{X} = \text{Br}, \text{Cl}$ ), but, for  $\text{X} = \text{F}$ , the order is  $\{\text{cyclo}(\text{Gly})_6-\text{X}^-\} > \{\text{cyclo}(\text{Gly})_8-\text{X}^-\} > \{\text{cyclo}(\text{Gly})_4-\text{X}^-\}$  due to the strong electrostatic interactions between H and  $\text{F}^-$ . Considering the large difference of the binding energy value illustrated in Table 1 and Table 2, the cyclopeptides should have the potential application as ions extractant.

TABLE 2: The bond length (nm) and binding energy ( $\text{kJ}\cdot\text{mol}^{-1}$ ) of  $\{\text{cyclo}(\text{Gly})_n-\text{X}^-\}$ .

Complex	X-H	N-H	H-Bond	Binding energy
$\{\text{cyclo}(\text{Gly})_4-\text{F}^-\}$	0.144	0.108	0.249	394.185
$\{\text{cyclo}(\text{Gly})_4-\text{Br}^-\}$	0.228	0.104	0.325	139.792
$\{\text{cyclo}(\text{Gly})_4-\text{Cl}^-\}$	0.222	0.104	0.317	115.136
$\{\text{cyclo}(\text{Gly})_6-\text{F}^-\}$	0.186	0.102	0.288	541.121
$\{\text{cyclo}(\text{Gly})_6-\text{Br}^-\}$	0.244	0.102	0.346	276.245
$\{\text{cyclo}(\text{Gly})_6-\text{Cl}^-\}$	0.240	0.102	0.341	219.198
$\{\text{cyclo}(\text{Gly})_8-\text{F}^-\}$	0.153	0.107	0.257	531.038
$\{\text{cyclo}(\text{Gly})_8-\text{Br}^-\}$	0.230	0.103	0.331	287.230
$\{\text{cyclo}(\text{Gly})_8-\text{Cl}^-\}$	0.221	0.103	0.322	246.257

TABLE 3: Orbital overlap population of  $\{\text{cyclo}(\text{Gly})_n-\text{X}^-\}$  and  $\{\text{cyclo}(\text{Gly})_n-\text{M}^+\}$ .

Complex	$\text{M}^+-\text{O}$ (e)			$\text{X}-\text{H}$ (e)		
	$\text{Li}^+$	$\text{Na}^+$	$\text{K}^+$	$\text{F}^-$	$\text{Br}^-$	$\text{Cl}^-$
$n = 4$	0.175	0.117	0.07	0.276	0.224	0.195
$n = 6$	0.652	0.502	0.317	0.378	0.341	0.296
$n = 8$	0.502	0.458	0.299	0.246	0.212	0.196

TABLE 4: The quantity of electricity of anion  $\text{X}^-$  in  $\{\text{cyclo}(\text{Gly})_n-\text{X}^-\}$ .

$\text{Cyclo}(\text{Gly})_n$	Atomic charges (e)		
	$\text{F}^-$	$\text{Br}^-$	$\text{Cl}^-$
$n = 4$	-0.578	-0.716	-0.768
$n = 6$	-0.526	-0.604	-0.683
$n = 8$	-0.548	-0.659	-0.727

**3.3. Mulliken Electron Population.** The strength of the covalent bond between the two atoms A and B can be obtained from the Mulliken electron population analysis [27–29]. If the overlapping electron has a large population between A and B, the covalent bond between the two atoms A and B will be stronger, the binding energy will have a larger value, and the compound should be more stable. The electron overlapping populations were shown in Table 3.

It can be found that the electron overlapping population value has the order of  $\text{cyclo}(\text{Gly})_n-\text{Li}^+ > \text{cyclo}(\text{Gly})_n-\text{Na}^+ > \text{cyclo}(\text{Gly})_n-\text{K}^+$  and  $\text{cyclo}(\text{Gly})_n-\text{F}^- > \text{cyclo}(\text{Gly})_n-\text{Br}^- > \text{cyclo}(\text{Gly})_n-\text{Cl}^-$ . This order is the same as the order of the binding energy (see Figures 5 and 7) and the distance of  $\text{M}^+-\text{O}$ .

In addition, it is very interesting that the order of the binding energy is  $\text{cyclo}(\text{Gly})_n-\text{F}^- > \text{cyclo}(\text{Gly})_n-\text{Br}^- > \text{cyclo}(\text{Gly})_n-\text{Cl}^-$  and the order of the electron overlapping populations is  $\text{F}^- > \text{Br}^- > \text{Cl}^-$ ; this is different from the order of the distance of the  $\text{X}^--\text{H}$  and the order of the three atoms F, Cl, and Br in periodic table. Therefore, we carried out the electric quantity calculation of the three halogen ions and cyclopeptides. From the analysis of the data in Table 4, the anion  $\text{Br}^-$  has more electrons than  $\text{Cl}^-$  and the order of the electronic quantity is  $\text{F}^- > \text{Br}^- > \text{Cl}^-$ . Considering the electrostatic interactions between negatively charged  $\text{X}^-$  and

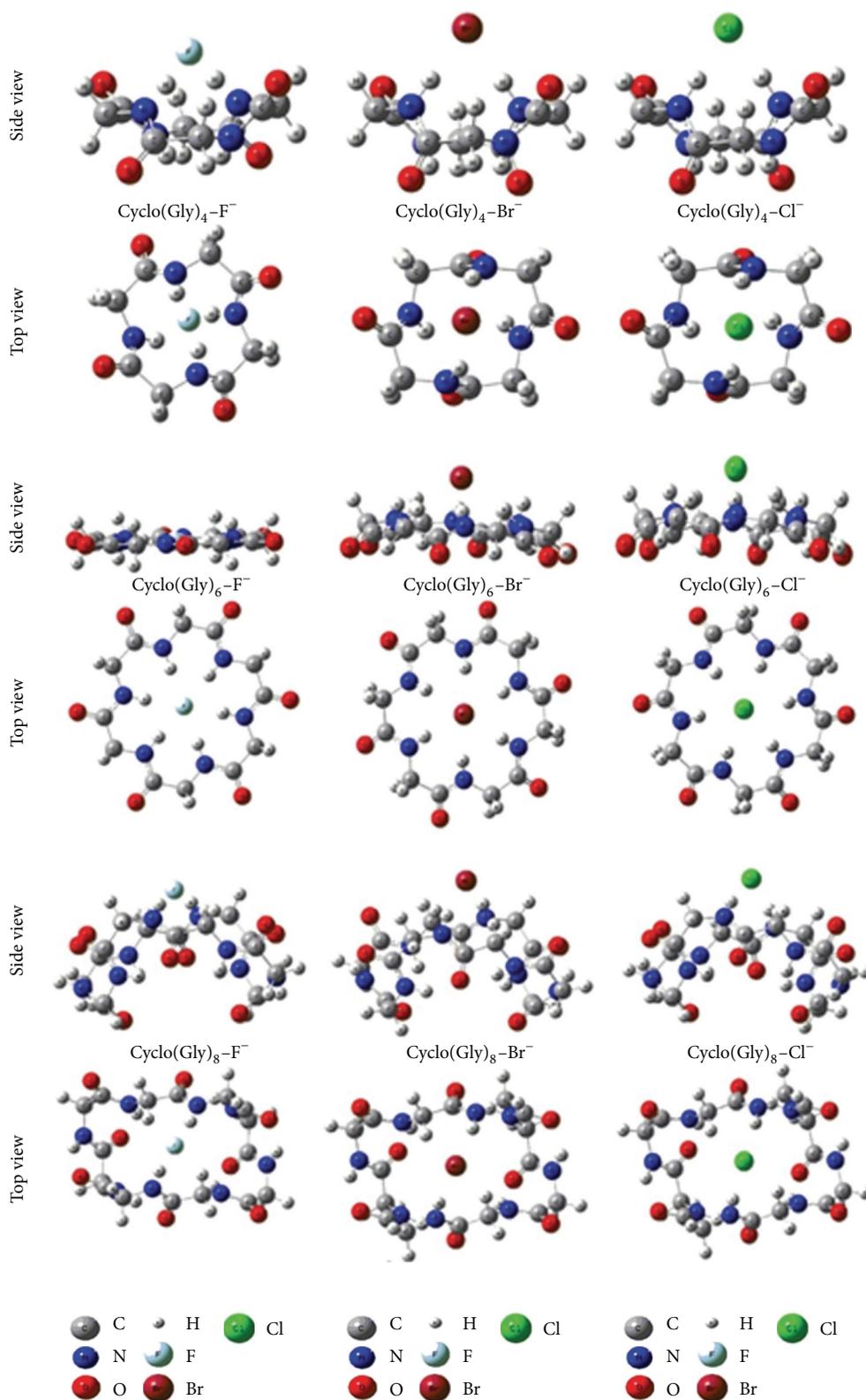


FIGURE 3: The optimizing conformation of cyclopeptide with  $F^-$ ,  $Cl^-$ , and  $Br^-$ . The side view and top view structure of all of the complexes were presented for better geometry understanding.

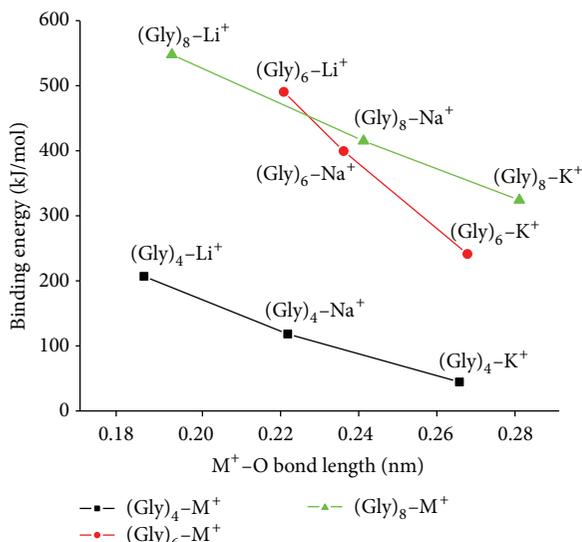


FIGURE 4: The relationship between the  $M^+ - O$  bond length and the binding energy of  $\{\text{cyclo}(\text{Gly})_n - M^+\}$ .

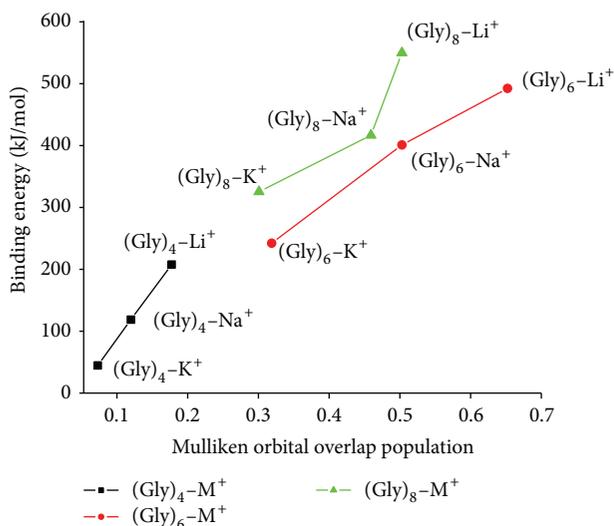


FIGURE 5: The relationship between the orbital overlap population and the binding energy of  $\{\text{cyclo}(\text{Gly})_n - M^+\}$ .

positively charged amino  $H^+$  atoms, the abnormal order of binding energy can be expected [14, 22].

#### 4. Conclusions

The cyclopeptides as ion nanocarriers for cations ( $Li^+$ ,  $Na^+$ , and  $K^+$ ) and anions ( $F^-$ ,  $Cl^-$ , and  $Br^-$ ) were studied carefully by theoretical calculation. The optimum conformation of cation-cyclopeptides and anion-cyclopeptides complexes was obtained by HF/STO-3G method and then further optimized at B3LYP/6-31G level. Both the cation and anion have a strong interaction with the cyclopeptide indicating that the cyclopeptides can act as amphi-ions carriers. The binding energy has the order of  $\text{cyclo}(\text{Gly})_n - Li^+ >$

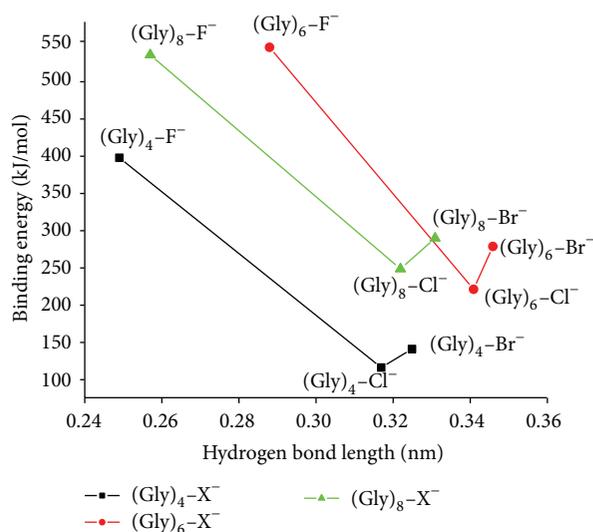


FIGURE 6: The relationship between the hydrogen bond length and the binding energy of  $\{\text{cyclo}(\text{Gly})_n - X^-\}$ .

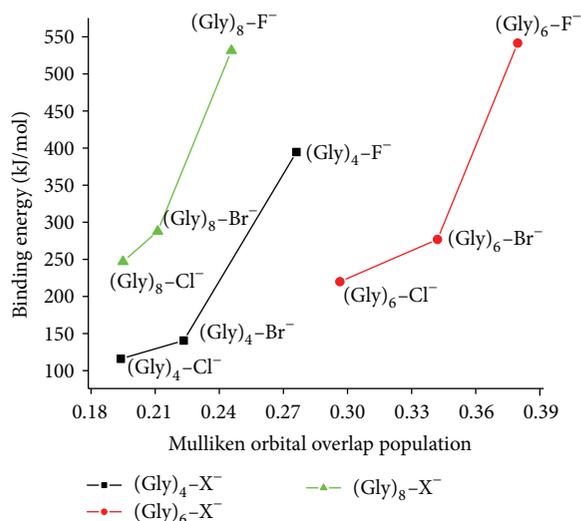


FIGURE 7: The relationship between the orbital overlap population and the binding energy of  $\{\text{cyclo}(\text{Gly})_n - X^-\}$ .

$\text{cyclo}(\text{Gly})_n - Na^+ > \text{cyclo}(\text{Gly})_n - K^+$  and  $\text{cyclo}(\text{Gly})_n - F^- > \text{cyclo}(\text{Gly})_n - Br^- > \text{cyclo}(\text{Gly})_n - Cl^-$  for the different cyclopeptide. For cation ions  $Li^+$ ,  $Na^+$ , and  $K^+$ , the binding energy of the different cyclopeptide is  $\{\text{cyclo}(\text{Gly})_8 - M^+\} > \{\text{cyclo}(\text{Gly})_6 - M^+\} > \{\text{cyclo}(\text{Gly})_4 - M^+\}$ . For anions  $Br^-$  and  $Cl^-$ , the binding energy has an order of  $\{\text{Cyclo}(\text{Gly})_8 - X^-\} > \{\text{cyclo}(\text{Gly})_6 - X^-\} > \{\text{cyclo}(\text{Gly})_4 - X^-\}$ ; for  $F^-$ ,  $\{\text{cyclo}(\text{Gly})_6 - F^-\} > \{\text{cyclo}(\text{Gly})_8 - F^-\} > \{\text{cyclo}(\text{Gly})_4 - F^-\}$  due to the strong electrostatic interactions between hydrogen bond and  $F^-$ . The different value of the binding energy illustrated that the cyclopeptide should have the potential application as ions extractants.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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