Novel Amphi-Ionophores

Kwang S. Kim,* Chunzhi Cui, and Seung Joo Cho

Department of Chemistry, Center for Biofunctional Molecules, Pohang University of Science and Technology, San 31, Hyojadong, Pohang 790-784, Korea

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The interactions of cyclic peptides containing glycines with cations (Li^+, Na^+, Be^{2+}, Mg^{2+}) and anions (F^- and Cl^-) have been investigated using ab initio calculations. The cyclic peptides are found to be exciting *novel* amphi-ionophores which show strong affinities for both cations and anions. In the presence of a cation, the C═O groups orient toward the center, whereas in the presence of an anion, the N−H groups do so. To our knowledge, we believe that these cyclic peptides are the first amphi-ionophores reported in the literature. Since there are few ionophores for anions, the cyclic peptides would be important anionophores in that they have large anion affinities. Although the individual amide group is rigid, the entire cyclic structures are very flexible, resulting in amphi-ionophores. If glycines are substituted by other residues, it could be utilized to design cyclic peptide ionophores to show different selectivities for cations and anions with varying flexibilities.

Host−guest complexation plays a central role in biological processes, such as ion-transfer, enzyme catalysis, and inhibition.[1] In order to elucidate the crucial nature of complex host-(protein)−guest(ions or organic molecules) interactions in biological processes, various experimental[2] and theoretical[3] studies have been done. To design useful ionophores, various important concepts such as host−guest size complementarity, rigidity of host molecule, and ion dipolar moiety orientations in host−guest complexes have been proposed.[4] Considering that real biological hosts are mainly proteins which are polypeptides, it is more desirable to mimic proteins with compounds comprised mainly of peptide bonds. In recent years cyclic polypeptides have been synthesized and used as inhibitors and antagonists.[5] Considering that more than a quarter of all known enzymes require the presence of metal atoms for full catalytic activity, we have performed an ab initio study of the interactions between cyclic peptides and ions, which may have much theoretical and practical importance. To our knowledge, this is the first ab initio study concerning cyclic peptides. In the present study, we investigate a cyclic tetrapeptide (**1**) and a cyclic hexapeptide (**2**) which contain only glycines. Although a number of cyclic polypeptides were reported,[5] no cyclic peptide containing only glycines has been reported in the literature. Since this structure exhibits good flexibility, it may show amphi-ionophore characteristics, which will be discussed below.

All the structures of compounds **1** and **2** and their ion complexes were fully optimized by Hartree−Fock (HF) calculations. The 6-31+G* (5d) basis set was employed. Calculations based on density functional theory (DFT) employing Becke's three parameter hybrid method using the Lee−Yang−Parr correlation functional (B3LYP) were also performed at the HF/6-31+G* optimized geometries for both **1** and **2**, and second-order Möller−Plesset perturbation (MP2) calculations were performed for **1**.[6] Basis set superposition error corrections (BSSEC)[7] are given for HF results. Frequency calculations carried out at the HF/3-21G level showed that all the structures are minima of the energy hypersurface. The MP2 and DFT-(B3LYP) energies are close to the HF energies. In the forthcoming discussion, for consistency, comparisons are done using the binding energies evaluated at the HF/6-31+G* level.

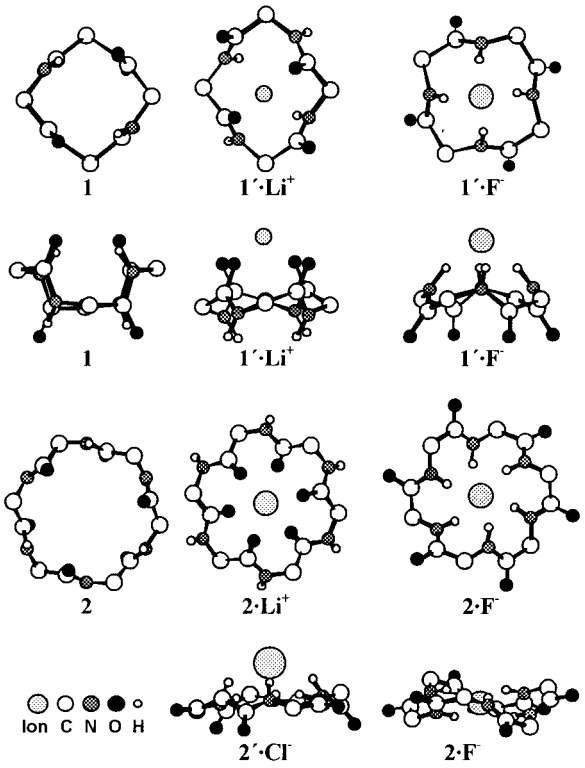

Figure 1. Selected structures of cyclic peptides and their ion complexes (top views in first and third rows and side views in second and fourth rows). H atoms in methylene groups are removed to improve visualization.

In structures **1** and **2**, both carbonyl and amide groups are nearly on the same cylindrical surface, i.e., nearly parallel to the principal axis (Figure 1). Upon complexation with an ion, the cyclic peptides are found to have two types of binding: one at the center and the other above the molecular plane. The former complex will be denoted as **n·I**, where **n** = **1** or **2** and

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TABLE 1: Binding Energies and Selected Geometrical Parameters[a]

	sym	HF(BSSEC)	MP2	DFT	I···O/H (Ct···O,Ct···H)	$\phi(\phi')$
1	S_4	0.0	0.0	0.0	(2.700,2.251)	130.9
1′·Li$^+$	C_2	65.7(64.8)	66.5	63.6	1.849, 2.964	38.5, 89.0
1′·Na$^+$	C_4	47.8(46.3)	48.2	46.1	2.413	59.8
1′·Be^{2+}	C_1	361.6(359.8)	359.4	366.5	1.550, 1.554, 1.578, 3.623	51.1, 52.5, 73.6, 106.5
1′·Mg^{2+}	C_4	234.9(232.3)	233.0	237.0	2.045	58.8
1′·F$^-$	C_4	59.5(57.9)	59.8	63.4	1.803	(17.0)
1′·Cl$^-$	C_4	29.2(28.7)	36.0	33.2	2.450	(14.9)
2	S_6	0.0		0.0	(3.443,3.688)	107.5
2·Li$^+$	S_6	105.3(103.1)		98.1	2.251	68.1
2·Na$^+$	S_6	86.2(83.1)		80.9	2.382	72.3
2·Be^{2+}	C_1	444.2(441.7)		446.9	1.603, 1.643, 1.659, 1.678, 3.297, 3.317	20.3, 49.3, 53.3, 71.1, 97.0, 95.5
2·Mg^{2+}	S_6	330.6(326.7)		326.5	2.132	62.6
2·F$^-$	C_i	84.1(81.5)		88.9	1.856	(32.0)
2′·Cl$^-$	C_3	40.2(39.5)		44.0	2.568, 2.682	(30.1, 37.2)

[a] Energies are in kcal/mol; distances in angstroms; angles in degrees. Ct denotes the center of an ionophore. See the text for notations.

I denotes an ion, and the latter complex as **n′·I**. In **n·I**, **n** keeps almost the original cyclic peptide structure, while in **n′·I**, **n′** has a volcano-like structure in which all the carbonyl O atoms (in the presence of a cation) or all amide H atoms (in the presence of an anion) are present on the crater with the ion **I** located above (Figure 1). From Figure 1, it is exciting to see spectacular changes in structures between cation and anion bindings. In the presence of a cation, carbonyl dipole moieties tend to point inward (toward the cation), while amide dipole moieties point outward. On the other hand, in the presence of an anion, the opposite trend is observed.

Table 1 lists the predicted binding energies, geometrical parameters of distances (I···O/H) between an ion I and O or H atoms (carbonyl oxygen atom for cation binding and amide hydrogen atom for anion binding), and the supplementary angles (ϕ/ϕ') of I···O═C/I···H−N. Upon binding with a cation (Li^+, Na^+, Be^{2+}, or Mg^{2+}), **1** does not have the structure of S_4 symmetry, but changes drastically to a volcano structure of symmetry C_4 or the like which has four (or two or three) oxygen atoms on the crater with the cation located above. On the other hand, upon binding with an anion (F^- and Cl^-), **1** also changes to a volcano structure of symmetry C_4, but in this case the crater is composed of amide hydrogen atoms instead of carbonyl oxygen atoms. In the case of crown ethers and starands, the ion dipolar moiety orientations (i.e., the supplementary angle ϕ of I···O═C) play a very important role in the host−guest complexation,[4d−e] and this turns out to be true for the cyclic peptides. In the cases of **1′·Na**$^+$ and **1′·Mg**$^{2+}$, the complex structures have C_4 symmetry; the I···O distances are 2.41 and 2.05 Å, respectively, and the angles ϕ are 60° and 59°, respectively. If an ion has a small radius, i.e., if the I···O distance is small enough to make the angles ϕ for the ion dipolar moiety orientations become very large (more than 80°) under symmetry C_4, the molecule is highly destabilized (by more than 10 and 20 kcal/mol for mono- and divalent ions, respectively). Then, instead of all four O atoms participating in the binding equivalently, only two or three O atoms participate in the ion binding so as to have reasonably small ϕ, while the remaining O atoms are farther from the ion so that even large values of ϕ cannot destabilize the molecule significantly. Therefore, in the cases of **1′·Li**$^+$ and **1′·Be**$^{2+}$, the complex structures have C_2 and C_1 symmetries, respectively; the I···O distances are 1.85 Å (for two O atoms) and 1.55−1.58 Å (for three O atoms), respectively, and the angles ϕ are 39° and 51−74°, respectively. The binding energies are 66 kcal/mol for **1′·Li**$^+$, 48 kcal/mol for **1′·Na**$^+$, 362 kcal/mol for **1′·Be**$^{2+}$, and 235 kcal/mol for **1′·Mg**$^{2+}$. In the case of the anion binding, the distances between the anion and four amide H atoms are 1.80 Å for **1′·F**$^-$ and 2.45 Å for **1′·Cl**$^-$, and the corresponding angles ϕ' are 17° for **1′·F**$^-$ and 15° for **1′·Cl**$^-$. The binding energies are 60 kcal/mol for **1′·F**$^-$ and 29 kcal/mol for **1′·Cl**$^-$.

Cyclic hexapeptide **2** seems to favor the central binding of cations, Li^+, Na^+, Be^{2+}, or Mg^{2+}. The cation is within the cavity comprised of six carbonyl O atoms. In this case the angle ϕ also plays an important role in maximizing the host−guest interaction. The binding energies for **2·Li**$^+$, **2·Na**$^+$, **2·Be**$^{2+}$, and **2·Mg**$^{2+}$ are 105, 86, 444, and 331 kcal/mol, respectively. In case of 18-crown-6 which is a well-studied host, the binding energies with Li^+, Na^+, and Mg^{2+} are 89, 82, and 287 kcal/mol, respectively.[3d] The binding energies of [l_6] starand with Li^+, Na^+, Be^{2+}, and Mg^{2+} are 93, 66, 389, and 239 kcal/mol, respectively.[4e] Therefore, the cyclic hexapeptide is found to be a better ionophore than 18-crown-6 and [1_6]starand at least in the gas phase in terms of the caion affinity. In a future study, it would be interesting to compare the affinities of all the three ionophores in solution, in consideration of the entropic effect on the cation binding due to the solvation of the ionophores as well as their conformational flexibility.

When binding with F^-, **2** prefers a central binding: **2·F**$^-$. In this case, the binding energy is 84 kcal/mol, the I···H distance between F^- and H(N) is 1.86 Å, and the angle ϕ' is 32°. Upon binding with Cl^-, **2** does not retain its original structure of S_6 symmetry but changes drastically to a volcano structure with C_3 symmetry having six amide H atoms on the crater with Cl^- located above. In **2′·Cl**$^-$, the Cl$^-$···H(N) distances are 2.57 Å for three H atoms and 2.68 Å for the remaining three H atoms, with angles ϕ' equal to 30° and 37°, respectively. The binding energy with Cl^- is 40 kcal/mol. Although intense efforts have been devoted to studies of anion complexation and recognition and of selective anion receptors such as calix[4]pyrrols and cage compounds,[8] the development of anion molecular recognition agents has been limited. In this regard, the cyclic peptides are interesting anionopohores with large binding affinities for anions.

As a result, the cyclic peptides are found to be exciting *novel* amphi-ionophores which show strong affinities for both cations and anions. In the presence of a cation, the C═O groups orient toward the center, whereas in the presence of an anion, the N−H groups orient toward the center. To our knowledge, we believe that this is the first amphi-ionophore reported in the literature. Although the individual amide group is rigid, the entire cyclic structures are very flexible, resulting in amphi-ionophores. If

glycines are substituted by other residues, it could be utilized to design cyclic peptide ionophores to show different selectivities for cations and anions with varying flexibilities. Consequently, it is not surprising that nature uses polypeptides to help and promote many physicochemical processes of living systems.

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Supporting Information Available: HF/6-31+G* optimized geometries and energies of **1** and **2** and those of their ion complexes (7 pages). Ordering information is given on any current masthead page.

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