Cation Affinities of Cyclohexadepsipeptide: Ab Initio Study

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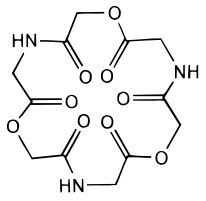
The interactions of cations (Li^+, Na^+, Be^{2+}, Mg^{2+}) with a cyclohexadepsipeptide composed of glycines and glycolic acids have been investigated using ab initio calculations. The crucial role played by the orientation of the ion−dipolar moiety could possibly explain the binding preference upon complexation with alkali cations since the dipole moment of the amide carbonyl moiety is greater than that of the ester carbonyl moiety. We find that cations prefer to bind amide carbonyl oxygen atoms rather than ester oxygen atoms. This should also explain why the binding affinities of the cyclohexadepsipeptide for cations are larger than those of 18-crown-6 and [1_6]starand in the gas phase. However, in divalent cationic cases which have twice the charge of the monovalent cationic species, the coordination numbers related to charge−charge interactions tend to be somewhat more important than the ion−dipolar moiety interactions. The self-consistent reaction field (SCRF) results for hexahydrated complexes of Na^+ with the cyclohexadepsipeptide indicate that cations prefer to bind amide carbonyl oxygen atoms rather than ester oxygen atoms in solution as well as in the gas phase. The complexation of two cyclohexadepsipeptide molecules with one cation (i.e., 2:1 sandwich-type complexes) in the gas phase has also been discussed to affirm the possible existence of such complexes suggested by Ovchinnikov. In these complexes, a cation binds mainly amide carbonyl oxygen atoms. If glycines and glycolic acids are replaced by other residues, these modified cyclodepsipeptide ionophores could show different selectivities for cations with varying flexibilities.

I. Introduction

Cyclodepsipeptides are often present in biological systems (such as valinomycin, enniatins, beauvericin), many of which are complexing agents for alkali and alkaline earth metal cations.[1] Enniatins, which are kinds of cyclohexadepsipeptide, are antibiotics known to be active against gram positive and mycobacteria, and it is believed that their antibiotic action results from their ability to affect the transport of metal ions across biological membranes.[2] These antibiotics act as mobile carriers which ferry cations across cell membranes. It is suggested that many enniatins form 2:1 or 2:2 (host/cation) complexes with alkali or alkaline earth metal ions and their membrane-affecting activity is due to the formation of sandwich aggregates. The 2:1 (host/cation) complexes are assumed to be of a sandwich structure in which two macrocyclic hosts enclose a cation.[3] Ovchinnikov[3a] suggested that in enniatins containing both peptide units and ester links, a cation binds probably the amide carbonyl oxygen atoms instead of the ester carbonyl oxygen atoms. This is contrasted to the case of valinomycin[4] where a cation is octahedrally coordinated to six ester carbonyl groups, as its coordination with amide carbonyl oxygen atoms is disfavored due to the spatial hindrance by the *N*-methyl group. Though these experimental results are very interesting, some views which are only suppositions based on indirect experimental methods need further clarifications. Therefore, it is important to investigate their structures as well as binding energetics with cations and to investigate whether cations are bound to amide group oxygens (O_a) or to ester group oxygens (O_e). For this end, we employed theoretical approaches.

There have been a number of theoretical studies of ionophores including ab initio calculations, molecular mechanics, molecular dynamics, and Monte Carlo simulations, as well as experimental studies.[5−10] To design useful ionophores, various important concepts such as host−guest size complementarity, rigidity of host molecules, and ion−dipolar moiety orientations in host−guest complexes have been proposed.[1,9,10] Ab initio calculations are proved to be a powerful means for studying the intrinsic factors which influence the host−guest complexation. Here, we performed ab initio calculations of cyclohexadepsipeptide (**1**) containing only glycine and glycolic acid moieties using the Gaussian 94 suite[11] of programs. In addition to the study of the complexation of **1** with various small size cations (Li^+, Na^+, Be^{2+}, and Mg^{2+}), we investigated the difference in cationic affinity between amide carbonyl groups and ester carbonyl groups.



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II. Calculation Method

All the structures of cyclohexadepsipeptide **1** and the 1:1 ion complexes were fully optimized by Hartree−Fock (HF) calculations using the 3-21G and 6-31+G* basis set, respectively. Vibrational frequency calculations were also carried out at the HF/3-21G level for **1** and 1:1 complexes, and the thermal quantities for the corresponding complexes were calculated using HF/3-21G level frequency results. Basis set superposition error correction (BSSEC) was carried out at the HF/3-21G and HF/

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TABLE 1: Binding Energies of 1:1 Cation Complexes[a]

		HF/3-21G			HF/6-31+G*		
	sym.	$-\Delta E$ ($-\Delta E^B$)	$-\Delta H$ ($-\Delta H^B$)	$-\Delta G$ ($-\Delta G^B$)	$-\Delta E$ ($-\Delta E^B$)	$-\Delta H$ ($-\Delta H^B$)[b]	$-\Delta G$ ($-\Delta G^B$)[b]
1	C_1	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
1·Li$^+$a′	C_3	156.6 (131.0)	155.1 (129.5)	142.2 (116.6)	105.7 (104.2)	104.2 (102.7)	91.3 (89.8)
1·Na$^+$a′	C_3				80.0 (78.4)	79.7 (78.2)[c]	65.3 (63.7)[c]
1·Na$^+$	C_3	128.1 (92.2)	127.9 (92.0)	113.5 (77.6)	78.1 (75.5)	77.9 (75.3)	63.4 (60.8)
1·Be^{2+}a	C_3	489.3 (463.8)	485.9 (460.3)	471.5 (446.0)	428.0 (426.0)	424.6 (422.5)	410.2 (408.2)
1·Be^{2+}e	C_3	464.1 (439.3)	463.4 (438.6)	445.6 (420.8)	402.1 (400.0)	401.4 (399.3)	383.6 (381.5)
1·Mg^{2+}	C_3	386.3 (347.4)	385.1 (346.1)	367.9 (329.0)	309.0 (305.4)	307.8 (304.2)	290.6 (287.0)

[a] Energies are in kcal/mol. ΔE, ΔH, and ΔG are interaction energies, enthalpies, and free energies without BSSEC (298 K and 1 atm), respectively, while ΔE^B, ΔH^B, ΔG^B are the corresponding ones with BSSEC. Here, ΔE and ΔE^B are interaction energies without ZPE correction. [b] Thermal energies for complexes optimized at the HF/6-31+G* level are calculated using those at the HF/3-21G level. [c] Since structure **1·Na$^+$a′** was not located at the HF/3-21G level, the thermodynamic quantities of **1·Na$^+$a′** are calculated using the thermal energies of **1·Na$^+$a** under the assumption that the difference in thermal energies between **1·Na$^+$a′** and **1·Na$^+$a** is not large.

TABLE 2: HF/6-31+G* Predicted Geometrical Parameters of Cation−Cyclohexadepsipeptide Complexes

	r(M···O$_a$)	ϕ_a	r(M···O$_e$)	ϕ_e	r(M···N)	r(M···O)	r(O$_a$···O$_a$)	r(O$_e$···O$_e$)	r(H···H)	r(H···O$_e$)
1·Li$^+$a′	1.877	31.5	3.489	102.9	3.847	3.717	3.228	3.942	7.304	3.201, 4.179
1·Be^{2+}a	1.551	25.3	3.183	98.7	3.625	3.514	2.683	4.284	7.710	3.446, 4.571
1·Be^{2+}e	2.918	89.2	1.579	32.6	3.584	3.606	3.889	2.718	7.221	3.366, 3.954
1·Na$^+$a′	2.214	29.0	3.942	106.1	4.189	3.977	3.619	3.732	6.935	3.083, 3.869
1·Na$^+$	2.279	67.8	2.444	76.1	3.647	3.649	3.700	3.340	7.077	3.125, 3.960
1·Mg^{2+}	2.067	60.7	2.159	66.1	3.609	3.595	3.187	3.252	7.589	3.414, 4.242

[a] Distances are in angstroms; angles in degree. r(X···Y) denotes the distance between atom X and the neighbored atom Y. The notations of each atom are the following: M, a cation; O$_a$, amide carbonyl oxygen; O$_e$, ester carbonyl oxygen atom; N, amide nitrogen atom; O, ester alkoxyl oxygen atom; H, amide hydrogen atoms. ϕ_a and ϕ_e are the supplementary angle between the M···O$_a$ vector and the amide C=O group, and that between M···O$_e$ vector and the ester C=O group, respectively.

6-31+G* optimized geometries using the counterpoise method.[12] To consider the effect of solvation, hexahydrated systems of complexes between Na^+ and **1** have been investigated at the HF/3-21G level. Then, the SCRF method was employed to investigate the influence of bulk solvent using a dielectric constant $\epsilon = 80.0$ based on the Onsager model.[13] SCRF(HF)/3-21G calculations were carried out at the HF/3-21G geometries of hexahydrated systems. In our study of the complexation of **1** with cations, the amide and the ester carbonyl groups point to the opposite sides of the molecular plane from each other as in beauvericin (Figure 2).[14] The complexation of two cyclohexadepsipeptide molecules with one cation (i.e., 2:1 sandwich-type complexes) in the gas phase has also been investigated at the HF/3-21G level. For 1:1 complexes, the calculated enthalpies and free energies showed the same trends as the internal energies, and the results at the HF/3-21G level also showed the same trends as the ones at the HF/6-31+G* level (Table 1). Thus, the following discussions are based on results of geometrical parameters and binding energies evaluated at the HF/6-31+G* level unless otherwise specified (Table 2).

III. Results and Discussion

All the cation complexes of **1** have C_3 symmetry, whereas the uncomplexed cyclohexadepsipeptide **1** (Figure 1) has C_1 symmetry. The uncomplexed structure **1** of C_3 symmetry is a saddle point of order 2, which is less stable than that of C_1 symmetry by 6.2 kcal/mol. Compared to **1** of C_3 symmetry, two of three amide hydrogen atoms (H_N) in **1** of C_1 symmetry interact more strongly with the neighboring ester carbonyl oxygen (O_e) atoms, while the remaining H_N atom orients outside and all amide carbonyl oxygen atoms (O_a) are separated far from each other to decrease the Coulombic repulsion. In addition, improper dihedral angles of two amide nitrogen atoms become more planar to strengthen the π-conjugation. All these factors contribute to the stability of structure **1** of C_1 symmetry relative to that **1** of C_3 symmetry.

The cyclodepsipeptide **1** is found to have five types of binding sites for cations, of which three are internal binding sites inside the cavity surrounded by six carbonyl oxygen atoms and two are external binding sites outside the cavity (the number of binding sites, of course, depends on a specified cation). A complex in which a cation binds only three O_a atoms inside the cavity will be denoted as **1·Ma**, where "M" denotes a cation and "a" denotes amides. A complex in which a cation binds only three O_e atoms inside the cavity will be denoted as **1·Me**, where "e" denotes esters. A complex in which a cation binds all six carbonyl oxygen atoms inside the cavity will be denoted as **1·M**. In the case of the external binding, a cation binds either three O_a atoms or three O_e atoms outside the molecular cavity. The former complex will be denoted as **1·Ma′**, and the latter complex as **1·Me′**. We have located six structures of 1:1 complexes (**1·Li$^+$a′**, **1·Be^{2+}a**, **1·Be^{2+}e**, **1·Na$^+$a′**, **1·Na$^+$**, and **1·Mg^{2+}a**, respectively) at the HF/6-31+G* level. However, at the 3-21G level, **1·Na$^+$a′** could not be located as the Na^+ ion entered the cavity of **1** from outside without energy barrier. Vibrational frequency calculations showed that **1·Li$^+$a′**, **1·Be^{2+}a**, **1·Na$^+$**, and **1·Mg^{2+}a** are at the minima of the energy hypersurfaces, but **1·Be^{2+}e** is a saddle point of order 2. However, we stopped locating the local minimum related to **1·Be^{2+}e**

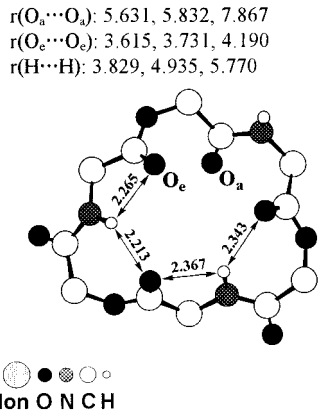


Figure 1. Structure and selected geometrical parameters of cyclohexadepsipeptide **1** of C_1 symmetry (distances in Å).

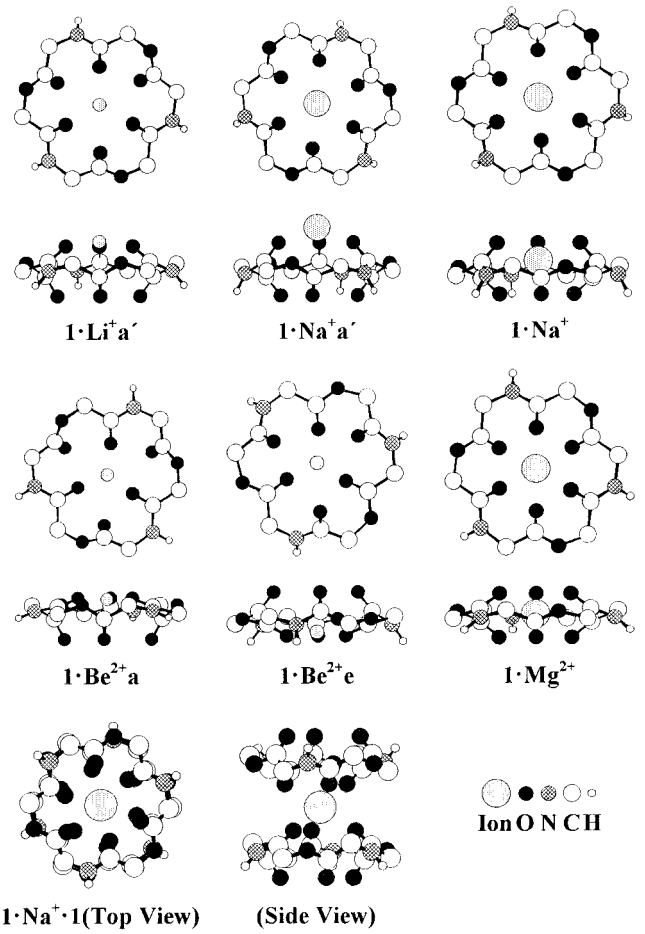


Figure 2. Structures of cation complexes of cyclodepsipeptide **1** (top views in 1st and 3rd rows and side views in 2nd and 4th rows). H atoms in methylene groups were removed to improve visualization.

because **1·Be^{2+}e** is less stable than **1·Be^{2+}a** and the magnitude of degenerate imaginary frequencies (18.1 i cm^{-1}) is very small.

In the case of Li^+, **1** has only one binding site (**1·Li$^+$a′**). Li^+ binds only three O_a atoms outside the cavity (Figure 2). Li^+ is bound externally to **1** at the distance of 0.22 Å from the plane of three O_a atoms along the C_3 axis, and the distance between Li^+ and O_a [r(M···O_a)] is 1.877 Å.[15] For **1·Li$^+$a′**, the supplementary angle ϕ_a for ∠M···O_a═C (where subscript "a" denotes amide) is 31.5°. This value, which is far less than 90°, shows that the O_a═C dipole has a relatively favorable orientation toward the Li^+ cation. We attempted to locate other binding sites of **1** for Li^+. But, when the Li^+ cation is around O_e atoms outside the cavity, it penetrates through the cavity and binds the O_a atoms outside the cavity (i.e., **1·Li$^+$a′**) without energy barrier.

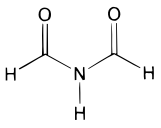
For Na^+, **1** has two binding sites: **1·Na$^+$a′** and **1·Na$^+$**, for which Na^+ is bound to three O_a atoms outside the cavity and to all six carbonyl oxygen atoms (i.e., three O_a and three O_e) inside the cavity, respectively (Figure 2). When a Na^+ cation is around O_e atoms outside the cavity, it enters into the cavity without energy barrier. For **1·Na$^+$a′**, the distances from Na^+ to O_a and O_e are 2.214 and 3.942 Å, respectively, and the angles ϕ_a and ϕ_e are 29.0° and 106.1°, respectively. For **1·Na$^+$**, the distances from Na^+ to O_a and O_e are 2.279 and 2.444 Å, respectively, and the angles ϕ_a and ϕ_e are 67.8° and 76.1°, respectively. The binding energy of Na^+ with **1** is 80.0 kcal/mol for **1·Na$^+$a′** and 78.1 kcal/mol for **1·Na$^+$**. It is interesting to note that the binding energy of the externally bound **1·Na$^+$a′** in which Na^+ is coordinated by three negatively charged oxygen atoms is 2 kcal/mol greater than that of the internally bound **1·Na$^+$** where Na^+ is coordinated by six oxygen atoms. This phenomena can be explained using the concept of ion−dipolar moiety orientations, since it is very similar to our particular study on the binding of Li^+ and Na^+ by [1_6]starand and 12-crown-4. In our previous study of crown ethers and starands, ion−dipolar moiety orientations were found to play an important role in the host−guest complexation.[16] For example, in the case of binding of Li^+ and Na^+ to [1_6]starands (which is a cyclic ionophore having spherical cavity comprised of six ketal oxygen moieties), the cations favor the external binding for the [1_6]-starand in which the cation is bound to three ketal oxygen atoms encompassing the upper part of the cavity (the lower part of the cavity is encompassed by the other three ketal oxygen atoms). The internal binding in which the cation is bound to all six ketal oxygen atoms is disfavored. When a cation is located at the center of the starand, the supplementary angle between the metal-to-oxygen vector and the dipole of the corresponding ketal moiety is more than 90°, resulting in very unfavorable energetics.[10f] In the case of 12-crown-4, the change is more drastic. Instead of binding a Na^+ cation at the center of the cavity comprised of the four ether oxygen atoms, the somewhat flexible 12-crown-4 structure drastically transforms itself into a hat structure with four oxygen atoms on the top so as to have favorable ion−dipolar moiety orientations with respect to the Na^+ cation located above the volcano (i.e., from a structure with S_4 symmetry to one with C_4 symmetry).[10f,17] Thus, it should be noted that the main factor affecting the preference of the external binding in the starand and 12-crown-4 is the ion−dipolar moiety orientations. For **1·Na$^+$a′**, the NBO[18] charge is 0.976 for Na^+, −0.831 for O_a, and −0.677 for O_e, respectively, the Coulombic interaction energy of Na^+ with three O_a atoms is −122 kcal/mol and that with six O_a, and O_e atoms is −177 kcal/mol. For **1·Na$^+$**, the NBO charges are 0.919 for Na^+, −0.778 for O_a and −0.733 for O_e, and the Coulombic interaction energy of Na^+ with six O_a/O_e atoms is −196 kcal/mol. The Coulombic interaction between Na^+ ion and oxygen atoms for **1·Na$^+$a′** is much less than that for **1·Na$^+$** and, thus, it hardly seems to explain the relative stability of **1·Na$^+$a′**. Therefore, we propose that the main reason for the preference of the external binding of **1** for Na^+ would be also due to better ion−dipolar moiety orientations, as is evident from the data of ϕ_a for **1·Na$^+$a′** and **1·Na$^+$**.

In the case of Be^{2+}, **1** has two binding sites: **1·Be^{2+}a** and **1·Be^{2+}e**, for which Be^{2+} is bound to three O_a atoms and to three O_e atoms, respectively. In both cases, Be^{2+} is inside the cavity surrounded by six carbonyl oxygen atoms (Figure 2). **1·Be^{2+}a** is 26 kcal/mol lower in energy than **1·Be^{2+}e**. The Be^{2+} ion is bound internally to **1** at a distance of 0.08 Å along the C_3 axis from the plane of three O_a atoms for **1·Be^{2+}a**, and it is of 0.18 Å from the plane of three O_e atoms for **1·Be^{2+}e**. The distance between Be^{2+} and O_a of **1·Be^{2+}a** (1.551 Å) is shorter than that between Be^{2+} and O_e of **1·Be^{2+}e** (1.579 Å). The supplementary angle ϕ_a for **1·Be^{2+}a** (25.3°) is smaller than the supplementary angle ϕ_e for **1·Be^{2+}e** (32.6°). All these differences are responsible for the better stability of **1·Be^{2+}a** over **1·Be^{2+}e**.

For Mg^{2+}, **1** is found to have one binding site (**1·Mg^{2+}**). Mg^{2+} is bound to all six ester and amide carbonyl oxygen atoms inside the cavity. The distance from Mg^{2+} to O_a and O_e is 2.067 and 2.159 Å, respectively.[19] The angles ϕ_a and ϕ_e are 60.7° and 66.1°, respectively. We also attempted to locate other binding sites of **1** for Mg^{2+}. However, when a Mg^{2+} cation is around either O_a or O_e atoms outside the cavity, it enters into the cavity without energy barrier. Thus, in the case of the complexation of Mg^{2+} with **1**, the coordination number seems to play a more important role than the ion−dipolar moiety orientations. This could be explained in the following way. The ratio of charge

to radius of Mg^{2+} is much greater than that for alkali metal ions, as it is a divalent cation. Therefore, the Mg^{2+} ion interacts more strongly with negatively charged oxygen atoms. It is evident from the deformation energy of the host which is a measure of energy difference between the fully optimized uncomplexed host and the deformed host upon compelxation with a cation. The deformation energy is 50.7 kcal/mol for **1·Mg^{2+}**, 51.0 kcal/mol for **1·Be^{2+}a**, and 59.7 kcal/mol for **1·Be^{2+}e**, while 18.4 kcal/mol for **1·Li^{+}a′**, 13.3 kcal/mol for **1·Na^{+}a′**, and 19.1 kcal/mol for **1·Na^{+}a**. Thus, the charge−charge interaction between a divalent ion and its coordinating O atoms seems to be more important than the charge−dipolar moiety interaction. It may be concluded similarly that a Be^{2+} ion binds oxygen atoms inside the cavity mainly due to the stronger charge−charge interaction. The reason the Li^{+} and Be^{2+} ions bind only three carbonyl O atoms of **1** seems to be due to their small size. To coordinate six carbonyl O atoms, they have to deform the host structure severely, and this will highly destabilize the complexes. For Li^{+}, the favorable orientation of the ion−dipolar moieties could have also played some role.

The binding energies of **1** with the corresponding cations for **1·Li^{+}a′**, **1·Na^{+}a′**, **1·Be^{2+}a**, and **1·Mg^{2+}** are 105.7, 80.0, 428.0, and 309.0 kcal/mol without BSSEC, respectively, and 104.2, 78.4, 426.0, and 305.4 kcal/mol with BSSEC, respectively. In the 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, at the HF/6-31+G* level (without BSSEC).[17] The binding energies of [1_6]starand with Li^{+}, Na^{+}, Be^{2+}, and Mg^{2+} are 93, 66, 389, and 239 kcal/mol, respectively, at the HF/6-31+G* level (without BSSEC).[10f] Therefore, the cyclohexadepsipeptide is found to be a better ionophore than 18-crown-6 and [1_6]starand in terms of the ion affinities in the gas phase.



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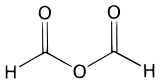

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The geometrical parameters and binding energies of all the complexes discussed above show that the cations favor binding sites around O_a atoms over those around O_e atoms. To elucidate the origin of this phenomena, it is necessary to investigate the binding affinities of amide and ester groups toward the cations. Thus, we studied the binding affinities of formic imide (**2**) and formic anhydride (**3**) for the cations at the HF/6-31+G* level. The binding energies of **2** with Li^{+}, Be^{2+}, Na^{+}, and Mg^{2+} are 66.7, 272.9, 49.1, and 160.5 kcal/mol, respectively. The corresponding binding energies of **3** are 55.2, 240.0, 39.8, and 136.2 kcal/mol, respectively. The binding energies for **2** are greater than those for **3** by 10−30 kcal/mol for all four cations. It seems that an amide carbonyl group has stronger affinity toward a cation than an ester carbonyl group. This is not because the charge−charge interaction between a cation and O_a is much greater than that between the cation and O_e (the NBO charges of O_a and O_e are −0.627 and −0.611, respectively), but because the charge−dipole moiety interaction by the amide carbonyl groups is much greater than that by the ester carbonyl groups (the dipole moments of **2** and **3** are 6.46 and 4.16 D, respectively). In **2**, the dipole moment vector of the NH moiety is in the same direction as that of the C=O moiety, while in **3**, the two dipole moment vectors are in the opposite direction. Therefore, the dipole moments of the amide carbonyl groups which are greater than those of the ester carbonyl groups are responsible for creating favorable binding sites around the amide carbonyl groups of **1** upon complexation with cations. In addition, since the dipole moments of the carbonyl groups of **1** are greater than those of the ketone carbonyl groups, the cationic affinities of **1** are greater than those of crown ethers and starands.

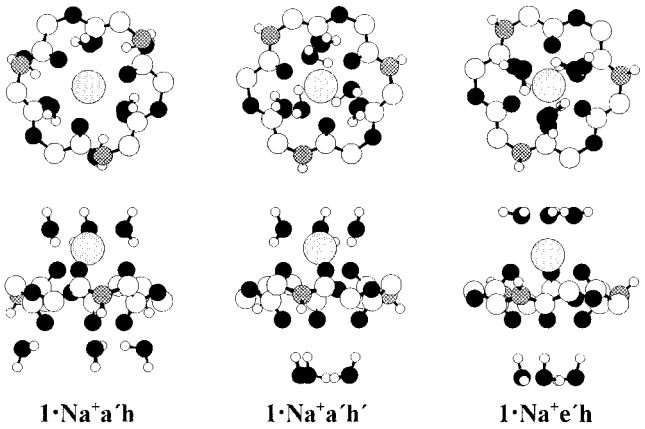

Figure 3. Structures of hexahydrated Na^{+} complexes of cyclodepsipeptide **1** (top views in 1st row and side views in 2nd row). H atoms in methylene groups were removed to improve visualization.

To consider the effect of solvation, we employed the SCRF method. To take into account a part of the first solvation shell structure, we first fully optimized hexahydrated complexes of **1** with Na^{+} (C_3 symmetry), hexahydrated Na^{+} ion (S_6 symmetry),[20] and nonhydrated **1** (C_1 symmetry) at the HF/3-21G level, and then carried out SCRF(HF)/3-21G calculations at the HF/3-21G optimized geometries (Figure 3). For hexa-hydrated complexes of **1** with Na^{+}, three water molecules are toward O_a sites, while the other three water molecules are toward O_e sites. The binding energies were evaluated by the following formula: $-\Delta E = E[Na^{+}\cdot(H_2O)_6] + E(\mathbf{1}) - E[\mathbf{1}\cdot Na^{+}\cdot(H_2O)_6]$. We have obtained three hydrated structures, and in all three complexes, the Na^{+} cation binds **1** outside the cavity and additionally three water molecules. In the first complex, Na^{+} binds three O_a atoms and three water molecules. Each of the remaining three water molecules involves hydrogen bonding interactions with an O_e atom and an amide H atom, and will be denoted as **1·Na^{+}a′h** ("h" denotes hydration). In the second complex, Na^{+} also binds three O_a atoms and three water molecules, but each of the remaining three water molecules involves hydrogen bonding interaction with an O_e atom and at the same time interacts with each other. It will be denoted as **1·Na^{+}a′h′**. In the last complex, Na^{+} binds three O_e atoms and three water molecules. Each of remaining three water molecules involves hydrogen bonding interactions with an O_a atom and interacts with each other. It will be denoted as **1·Na^{+}e′h**. The HF/3-21G binding energy of Na^{+} is 67.0 kcal/mol for **1·Na^{+}a′h**, 49.0 kcal/mol for **1·Na^{+}a′h′**, and 38.3 kcal/mol for **1·Na^{+}e′h**. The SCRF(HF)/3-21G binding energy of Na^{+} is 64.6 kcal/mol for **1·Na^{+}a′h**, 54.0 kcal/mol for **1·Na^{+}a′h′**, and 51.7 kcal/mol for **1·Na^{+}e′h**. Both HF/3-21G and SCRF(HF)/3-21G results reveal the same trends of binding preference that the Na^{+} cation prefers to bind amide carbonyl oxygen atoms outside the cavity over ester carbonyl oxygen atoms.

It is well-known that natural antibiotic beauvericin, enniatins A and B, which are kinds of cyclohexadepsipeptide, can also form complexes with alkali metals. These antibiotics act as mobile carriers ferrying cations across cell membranes. A study of the effects of enniatins on the conductivity of artificial lipid membranes in the presence of both mono- and divalent cations revealed that 2:1 (host:cation) complexes were probably formed. The above studies indicate that the 2:1 complexes are of a

TABLE 3: HF/3-21G Predicted Binding Energies (kcal/mol) of 2:1 Sandwich-Type Complexes Having a Cation Between Two 1's[a]

	1·Li^+·1	1·Na^+·1	1·Be^{2+}·1	1·Mg^{2+}·1
$-\Delta E$	196.0	184.6	542.1	477.1
$-\Delta E^B$	165.3	143.4	516.3	435.3

[a] $-\Delta E$ and $-\Delta E^B$ are binding energies without and with BSSEC.

sandwich structure in which two macrocyclic hosts enclose a cation.[3a] According to our calculational results for **1**, it seems that a cation favors the binding around O_a atoms more than O_e atoms. Li^+ and Na^+ favor the external binding for **1** (at the HF/631+G* level). At the HF/3-21G level, K^+ also favors the external binding for **1**.[21] In case of external binding, a cation coordinates only three oxygen atoms. Thus, it is possible for a cation to bind two host molecules (i.e., to form a 2:1 sandwich-type complex) and fulfill its coordination capacity. The 2:1 sandwich-type complex for **1** can therefore be expected to bind a cation mainly through amide carbonyl groups because of its intrinsic stronger affinity for cations than the corresponding ester carbonyl groups. Although Be^{2+} favors internal binding, considering the structure of its complex with **1**, it is possible for enniatins to form 2:1 sandwich-type complexes with Be^{2+} to have the advantage of favorable ion−dipolar moiety orientations in addition to charge−charge interactions. Our HF/3-21G calculations of the 2:1 complexes (C_3 symmetry) in the gas phase indicate that formation of such 2:1 sandwich-type complexes is energetically favored by a large magnitude. The BSSE-corrected binding energies for Li^+, Na^+, Be^{2+}, and Mg^{2+} are 165.3, 143.4, 516.3, and 435.3 kcal/mol, respectively (Table 3).

IV. Conclusions

The cyclohexadepsipeptide shows strong affinities for cations. It is a better host for cations than 18-crown-6 and [1_6]starand, at least in the gas phase in terms of cation affinity. Upon complexation with monovalent cations, the ion−dipolar moiety orientation is found to play a very important role in cyclohexadepsipeptide, while in the case of complexation with divalent cations, the charge−charge interactions seem to play a more important role than the ion−dipolar moiety interactions. An amide carbonyl group seems to have stronger affinity intrinsically than an ester group. Thus, a cation is more closely bound toward amide carbonyl oxygen atoms than an ester group in solution as well as in the gas phase. Since Li^+, Na^+, and Be^{2+} favor external (for Li^+ and Na^+) or near-external binding (for Be^{2+}), it would be possible that cyclohexadepsipeptides such as enniatins form 2:1 sandwich-type complexes to fulfill their coordination capacities, wherein a cation binds mainly with amide carbonyl oxygen atoms. Our calculation of the 2:1 complexes in the gas phase shows that the complex formation is energetically favored by a large magnitude. The design of cyclohexadepsipeptide ionophores with varying flexibilities showing different ion selectivities should be possible by suitable substitution of both the glycine and glycolic acid moieties.

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(15) In this case, the distance between two neighboring O_a atoms is 3.228 Å, that between neighboring two O_e atoms, 3.942 Å, and that between two H_N atoms, 7.304 Å. The distances between a H_N atom and every two neighboring O_e atoms are 3.201 and 4.179 Å, respectively. The distance between two neighboring O_a atoms is remarkably reduced by 1.3 Å, while others are increased compared to **1** of C_3 symmetry.

(16) When the supplementary angle is 0°, the orientation of the carbonyl group toward the metal cation is the most favorable. If the supplementary angle is 30°, the molecule is destabilized by ∼3 kcal/mol. For the supplementary angle of 90°, it is destabilized by 15−20 kcal/mol per moiety. If the angle is more than 70°, the structure is generally not stable enough.

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(19) The distances between two neighboring O_a atoms and that between two neighboring O_e atoms are 3.187 and 3.252 Å, respectively.

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(21) The binding energies of K^+ with **1** are 81.6 kcal/mol for **1**·K^+**a′**, 66.3 kcal/mol for **1**·K^+ (TS), and 76.0 kcal/mol for **1**·K^+**e′**.