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[3.2.1] and [4.1.1] isomers of Lehn's [2.2.2] Cryptand: Prediction of ion selectivity by quantum chemical calculations XV**

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Dedicated to Prof. Dr. Peter Klüfers on the occasion of his 70th birthday.

Selective alkaline and earth alkaline metal ion encapsulation by two different Lehn-type cryptands, noted as [3.2.1] and [4.1.1], was predicted and between them compared on the DFT (B3LYP/LANL2DZp) basis set. Since these cryptands are isomers to the well-known [2.2.2] cryptand, the cation encapsulation selectivity of all three cages were compared. The ion selectivity and ability of the host to adjust their structure to successfully accommodate the metal ions, were based on energy and geometric criteria. Different lengths of O-Et-O-bridging arms provide an unsymmetrical cryptand host with great flexibility to accommodate large alkali and alkaline earth metal cations.

Introduction

A great impact in field of supramolecular chemistry was made by J.-M. Lehn and his coworkers about 50 years ago by the discovery of 4,7,13,16,21,24-(hexaoxa-1,10-diazabicyclo-[8.8.8] hexacosane, today better known as [2.2.2] (Figure 1) and traded

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as Kryptofix 222.[1,2] The potential of [2.2.2] alike compounds to act as a host and to selectively bind guest species, in particular alkali and alkaline earth metal ions, was immediately recognized. This discovery granted Lehn together with Pedersen and Cram a Nobel Prize in 1987,[3] and to the field of supramolecular encapsulation chemistry the legacy to pursuit for optimizing and better understanding of the systems that represent it. Today some of these compounds have found their application in numerous fields, such as: phase-transfer catalysis,[4] selective complexation of radioactive or toxic ions in medicine,[5] studies on Zintl phases,[6] models for carrier-antibiotics such as Valinomycin and enzyme inhibitors,[7] and as a ligand for MRI contrast agents.[8] The unmatched selectivity of Lehn-type diaza-polyether cryptands for encapsulation of complementary sized metal cations guests[9] are attributed to great thermodynamic and kinetic stabilities.[10] The high thermodynamic stability of metal-cryptate complexes arises predominately from the high degree of preorganization and low degree of solvation of cryptands, such that their stability is enthalpic by origin.[11] The ligand's stringent selectivity preferences is often attributed to size complementarity considerations,[12] but also other factors such as ligand flexibility and coordination preferences of guests are recognized to have an important influence.[13]

In this contribution our focus was set to investigate the selective complexation of Lehn-type cryptands [3.2.1] and [4.1.1], and to compare them with already published results for the [2.2.2] cryptand[14] by means of computational chemistry. The cryptands [2.2.2], [3.2.1] and [4.1.1] are clearly isomers of each other. Structures of selected systems investigated in this work are displayed in Figure 1. It is worth noting that the cryptand hosts, besides increasing cavity volume, possess an evolution to form three-dimensional to more planar encapsulation environments considering the different lengths of the bridging linkers, going from [3.2.1] to [4.1.1], Figure 2.
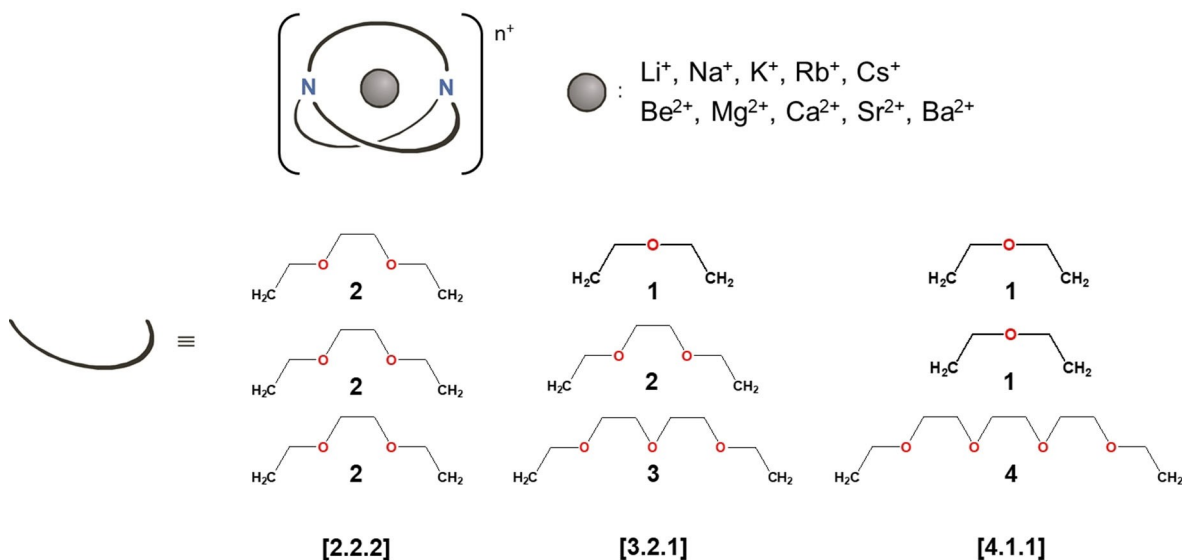
Figure 1. Schematic presentation of [2.2.2], [3.2.1] and [4.1.1] cryptands.
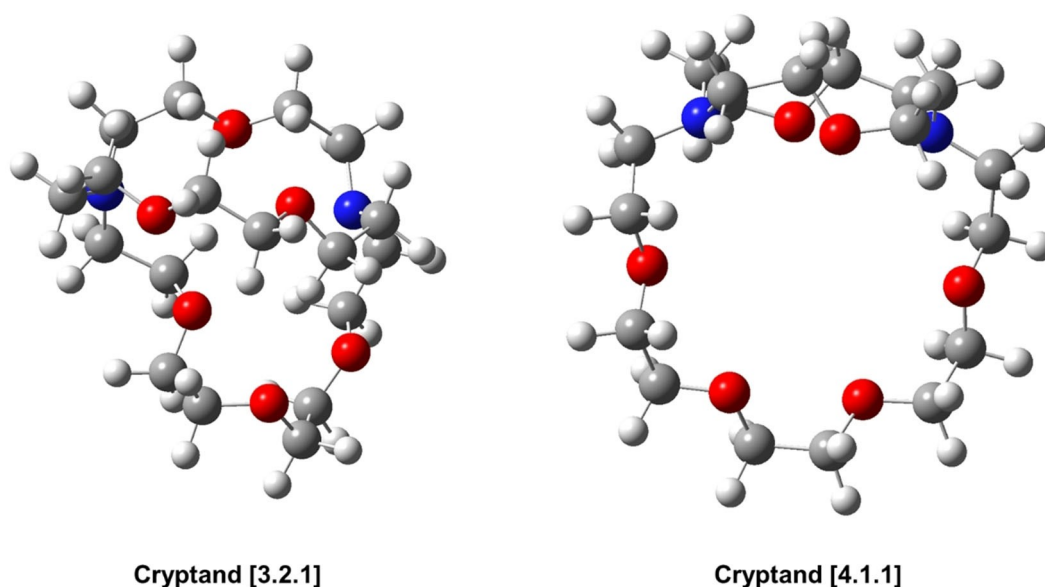

Figure 2. Calculated (RB3LYP/LANL2DZp) structures of cryptands [3.2.1] and [4.1.1].

Computational details

All here reported density functional calculations were performed at the hybrid B3LYP[15] theory level in combination with the LANL2DZ[16] basis set with effective core potentials, augmented with polarization functions on non-hydrogen atoms. This combination of the hybrid functional and basis set (further denoted as B3LYP/LANL2DZp) was selected since in earlier studies on selective ion complexation and related topics, we obtained results that were consistent with experimental values. The success of calculations at this level has been documented, and additionally permits comparison of the results of the current study with our earlier work.[17] By carrying out calculations of vibrational frequencies, all structures were characterized as minima on the potential energy surface with no imaginary frequencies. All calculations were performed without any implicit solvent model. Presented relative energies were corrected for zero-point vibrational energy. The calculations were performed using the GAUSSIAN16 suite of programs.[18]

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Results and Discussion

In the field of supramolecular chemistry to investigate the ability of Lehn-type cryptands to encapsulate small cations, two properties have been proven to be trustworthy criteria. Comparison of geometric changes of the host and changes in the system energy, upon hosting a guest molecule, of which

the changes in the energy of the system can be best monitored by constructing a model reaction (1), presented as follows:
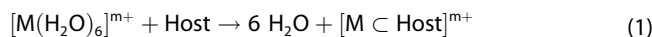
$$[M(H_2O)_6]^{m+} + Host \rightarrow 6\ H_2O + [M \subset Host]^{m+} \qquad (1)$$

All cations were calculated in a six-fold coordination environment of water molecules, as most reactions in bio-relevant chemistry are investigated in water, or in solvents that can be modeled by water molecules.[19] The *Host* in equation (1) represent here the investigated cryptands [3.2.1] and [4.1.1], for which the results for the computed complexation energies are reported in Table 1 and plotted against the cation radii[20] in Figure 3.

Examining the results obtained by applying Eqn (1), from all alkaline cations K$^+$ is forming the most stable complex with cryptand [3.2.1], closely followed by the Rb$^+$ cation. The cryptand [3.2.1] complex with Cs$^+$ has also a marginally low complexation energy compared to that of Na$^+$ and Li$^+$ cations, which are obviously too small to fit appropriately into the cryptand cavity. As for the alkaline earth cations, those with the larger cation radii (Ca^{2+}, Sr^{2+} and Ba^{2+}) liberate the highest complexation energy, from which the [Ba⊂[3.2.1]]$^{2+}$ complex can be pointed out as the most stable one. Smaller ions from this group like the Mg^{2+} cation, has the lowest complexation energy with the [3.2.1] cryptand (−3.72 kcal/mol). Be^{2+} as a smaller cation from this group, defies this trend and exhibits a significantly higher complexation energy (−10.26 kcal/mol)

Table 1. Calculated (B3LYP/LANL2DZp) complexation energies (E$_{com}$) for the systems presented in Figure 1 based on Eqn. (1).

Metal ions	R [Å]	E$_{com}$ [kcal mol^{-1}] [3.2.1]	[4.1.1]
Li$^+$ (C$_2$) (ts)	0.92	–	9.81
Li$^+$ (C$_1$)	0.92	10.47	8.49
Na$^+$	1.18	3.53	13.35
K$^+$	1.51	0.41	0.64
Rb$^+$	1.61	1.59	−1.70
Cs$^+$	1.74	2.40	−2.69
Be^{2+} (C$_2$) (ts)	0.45	–	1.33
Be^{2+} (C$_1$)	0.45	−10.26	−6.51
Mg^{2+}	0.89	−3.72	0.95
Ca^{2+}	1.12	−15.46	−10.82
Sr^{2+}	1.26	−14.52	−10.93
Ba^{2+}	1.42	−16.03	−10.04

C$_1$ and C$_2$ report the symmetry of the complexes, while all other [M⊂[3.2.1]] show C$_1$ and [M⊂[4.1.1]] show C$_2$ symmetry. ts: transition state, Ionic radii R: taken from ref. 20, E$_{com}$ complexation energies based on Eqn (1)
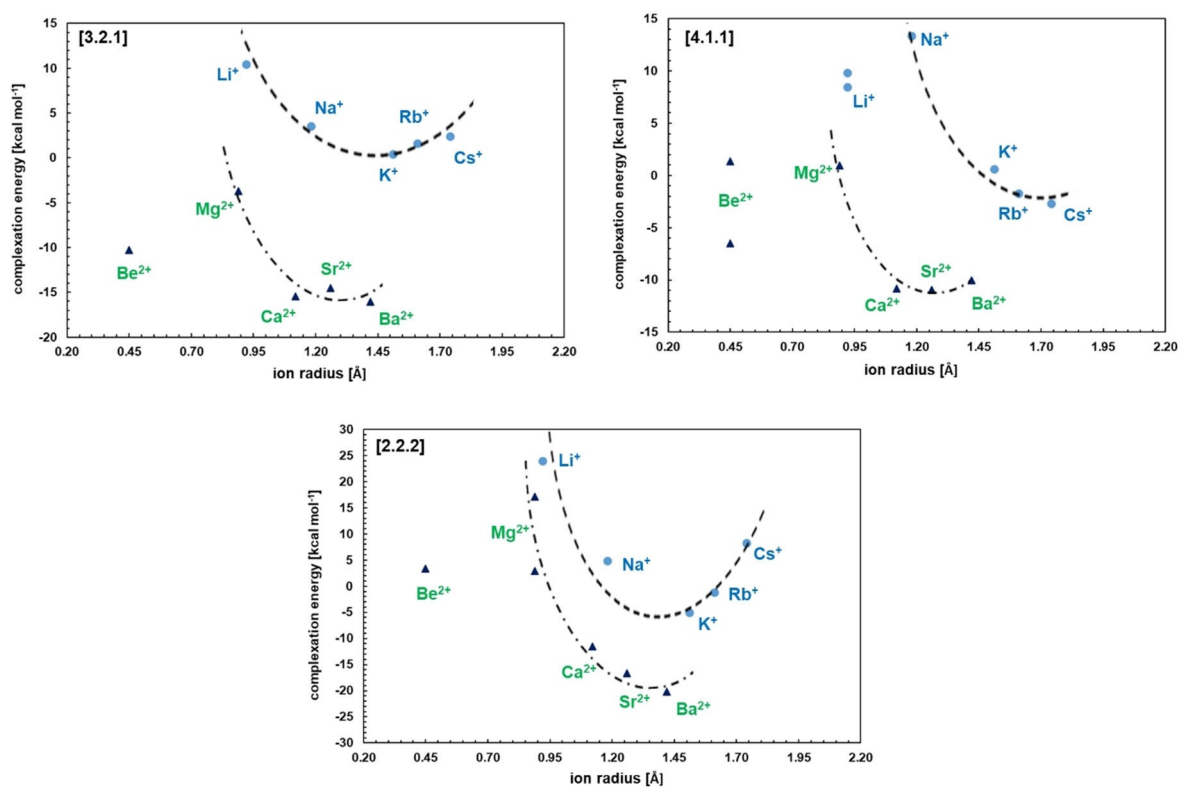

Figure 3. Calculated complexation energies (RB3LYP/LANL2DZp) according to Eqn. (1), for cryptands [2.2.2], [3.2.1] and [4.1.1], plotted against the ionic radius of M^{m+}; the dashed lines illustrate the trend in the relevant properties.

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compared to its size. In this case, Be^{2+} as a cation with the smallest radii has the freedom to find itself in a comfortable position inside the cryptand cavity, locating itself on one side of the cavity coordinated to the one nitrogen bridge head and one oxygen donor of every bridging arm.

Cryptand [4.1.1] compared to cryptand [3.2.1] has a sufficient larger cavity size. Therefore, its encapsulation abilities are favored for cations of larger radii. From the data in Table 1 for all the alkali metal cations, Cs^+ is best accommodated with the complexation energy of −2.69 kcal/mol. All the other alkali metals are too small to be appropriately accommodated into the cavity of cryptand [4.1.1], which is reflected in disfavored complexation energies (see Table 1). The first thing notable in Table 1 for [4.1.1], are the results regarding the small Li^+ cation, where the C_2 symmetric structure is the transition state for an inner molecular interchange type O-donor exchange in the Et-O-Et-O-Et-bridge, originating from the two outer O-donor atoms. This transition state leads to the C_1 minimum, where Li^+ is coordinated by three oxygen and the two nitrogen donors. From the alkaline earth cations, Ca^{2+}, Sr^{2+} and Ba^{2+} have distinguished themselves as the best suited for complexation with the cryptand [4.1.1]. Mg^{2+} falls into the category of being too small, whereas Be^{2+} leads to two structures. In the case of $[Li \subset [4.1.1]]^+$ the C_2 symmetric structure is a transition state, whereas in the case of $[Be \subset [4.1.1]]^{2+}$ this C_2 symmetric transition state connects the two local minima, where Be^{2+} is located and coordinated next to one bridge head N-atom. To traverse this transition state an activation barrier of 7.84 kcal/mol has to be overcome. All studied alkaline earth cations demonstrate lower complexation energies in comparison to alkaline metal cations. This is surely an artifact of the method due to their dicationic nature. The charge receives extra stabilization in the large supramolecular structures, which six water molecules cannot provide.

To compare the cation selectivity of the investigated cryptands [3.2.1] and [4.1.1] against the well-known [2.2.2] cryptand calculated at the same level of theory, by energies free of influences of solvents or reference complexes, model reactions (Eqns. (2) and (3)) were constructed:

$$[M \subset [2.2.2]]^{m+} + [3.2.1] \rightarrow [M \subset [3.2.1]]^{m+} + [2.2.2] \qquad (2)$$

$$[M \subset [2.2.2]]^{m+} + [4.1.1] \rightarrow [M \subset [4.1.1]]^{m+} + [2.2.2] \qquad (3)$$

Results obtained by application of Eqns. (2) and (3), are graphically displayed in Figure 4 in which the position of the cations above the dashed line are those that are better accommodated in cryptand [3.2.1] or [4.1.1], respectively. By comparison, the selectivity of the cryptands [3.2.1] and [4.1.1] against that of [2.2.2], the cations in the 'middle' of the group, by radii size criteria, are better encapsulated in the here investigated cryptands. In the case of [3.2.1] that would be K^+, Rb^+, Sr^{2+} and Ba^{2+}, whereas all the rest are obviously better stabilized in the environment of the [2.2.2] cryptand. As for the [4.1.1] cryptand, we have Rb^+ and Ca^{2+} cations as the marginally ones, where their stabilization can be equally accomplished by [4.1.1] or [2.1.1]. Cations Na^+, K^+, Sr^{2+} and Ba^{2+} in comparison to [2.2.2] are preferred by the [4.1.1] cryptand, whereas Li^+, Rb^+, Cs^+ and Be^{2+} are better suited for the [2.2.2] cryptand cavity.

Geometric properties can be summarized in bond distances between the encapsulated metal cation and the donor atom of the host (for cryptands [3.2.1] and [4.1.1] these are oxygen and nitrogen atoms). These geometric properties are summarized in Table 2 and are compared (at the same level of theory), with bond distances between the investigated cations and coordinated solvent molecules, e.g., water and ammonia (see Table 2). Results of this comparison can be best monitored in Figure 5 for cryptand [3.2.1] and Figure 6 for [4.1.1].

The bisecting lines in Figures 5 and 6 present the best alignment between the bond distances of the cryptand donor atoms to metal cation and solvent molecules to metal cation, e.g., where the coordination would most likely occur. The validity of this method depends on whether the donor atoms that coordinate to the metal ions are the same, or the donor and reference atoms are the same or of identical hybridization.[22] The ions above the line are somehow too small, whereas the ions below the line are too large for the
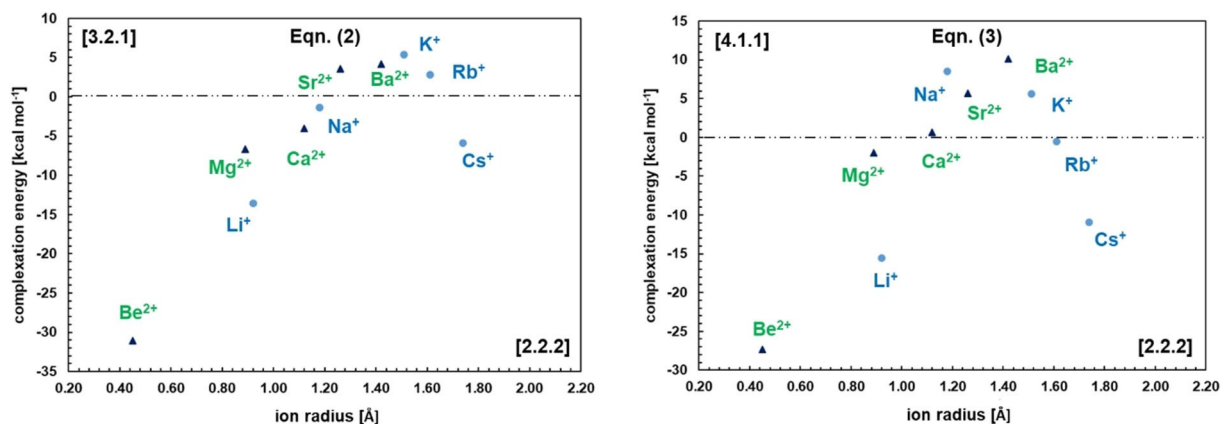

Figure 4. Calculated complexation energies (RB3LYP/LANL2DZp) according to Eqns. (2) and (3), plotted against the ionic radius of M^{m+}.

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Table 2. RB3LYP/LANL2DZp computed geometric parameters for [M⊂Host]$^{m+}$ complexes.

Metal ions	R[Å]	$d(M–O_{H2O})$ [Å]	$d(M–N_{NH3})$ [Å]	$d(M–O_{[3.2.1]})$ [Å]	$d(M–N_{[3.2.1]})$ [Å]	$d(M–O_{[4.1.1]})$ [Å]	$d(M–N_{[4.1.1]})$ [Å]
Li$^+$	0.92	2.11	2.13	2.09; 3.39; 4.08	2.58	2.18; 4.73	2.45
Na$^+$	1.18	2.40	2.67	2.52; 2.62	2.89	2.42; 3.39; 4.00	2.83
K$^+$	1.51	2.76	3.01	2.79; 2.87	3.01	2.88; 3.25	3.27
Rb$^+$	1.61	2.97	3.21	3.07	3.22	3.03; 3.21	3.38
Cs$^+$	1.74	3.20	3.45	3.25	3.38	3.21	3.45
Be^{2+}	0.45	1.85	1.77	1.68; 3.13; 3.53	1.86; 3.47	1.69; 3.14; 3.71; 4.01	1.87; 2.88
Mg^{2+}	0.89	2.10	2.29	2.18; 2.38	2.54; 2.87	2.11; 3.51	2.37
Ca^{2+}	1.12	2.43	2.63	2.55	2.80	2.53	2.77
Sr^{2+}	1.26	2.60	2.80	2.68	2.90	2.55	2.92
Ba^{2+}	1.42	2.80	3.00	2.88	3.05	2.95	3.19

Ionic radii R: taken from ref. 20; d(M–N$_{H2O}$) and d(M–N$_{NH3}$): taken from taken from ref. 21.
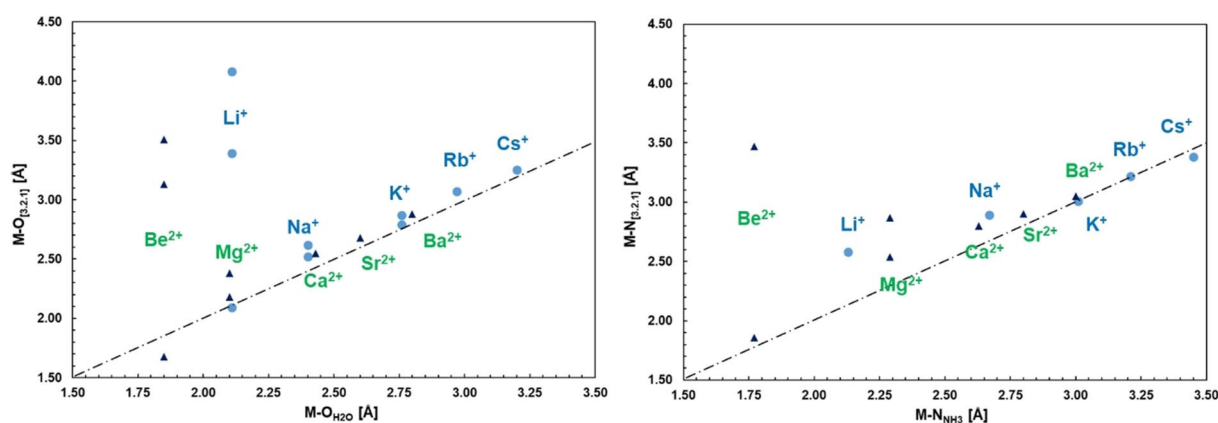
Figure 5. Calculated (RB3LYP/LANL2DZp) M–O$_{[3.2.1]}$ and M–N$_{[3.2.1]}$ distances in [M⊂[3.2.1]]$^{m+}$ plotted against the calculated (RB3LYP/LANL2DZp) M–O$_{H2O}$ and M–N$_{NH3}$ distances.
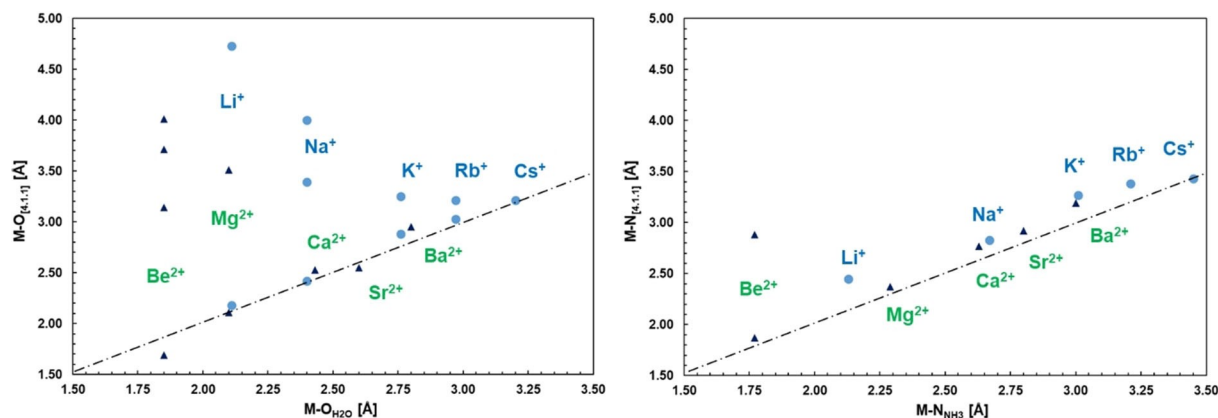
Figure 6. Calculated (RB3LYP/LANL2DZp) M–O$_{[4.1.1]}$ and M–N$_{[4.1.1]}$ distances in [M⊂[4.1.1]]$^{m+}$ plotted against the calculated (RB3LYP/LANL2DZp) M–O$_{H2O}$ and M–N$_{NH3}$ distances.

studied cryptand cage. In the case of the [3.2.1] cryptand, alkali cations K$^+$, Rb$^+$ and Cs$^+$, and alkaline earth metals Ca^{2+}, Sr^{2+} and Ba^{2+} are approximately close to the bisecting line. With the cations Li$^+$, Na$^+$, Be^{2+} and Mg^{2+} being too small (see Figure 5), which is consistent with the calculated complexation energy.

For cryptand [4.1.1], the cations Cs$^+$, Ca^{2+}, Sr^{2+} and Ba^{2+} are very close to the bisecting line, where the smaller ones (Li$^+$, Na$^+$, K$^+$, Rb$^+$, Be^{2+} and Mg^{2+}) are scattered mostly above the bisecting line (Figure 6). Notably, some cations possess more than one bond distance value between the cryptand donor

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atom and metal center (Figures 5 and 6), which is accompanied by a disfavored complexation energy. This is more pronounced for the smaller cations, which in regard to the larger ones are not placed in the center of the cryptand cavity, and in that way would be at an equal distance to all the donor atoms and so be stabilized by them. As mentioned before, smaller cations have the freedom to move around the larger cavity of the host. This can result in a significantly large complexation energy stabilization up to 7.90 kcal/mol, which was the case in complex $[Be \subset [4.1.1]]^{2+}$ where one coordination mode resulted in 1.33 kcal/mol, and the other in -6.57 kcal/mol complexation energy (see Table 1). This is especially the case in unsymmetrical cryptands such as [3.2.1] and [4.1.1].

An alternative point of view on cryptands is that they are bridged crown ethers. While the basis of [2.2.2] is the 18-crown-6 motive, [3.2.1] and [4.1.1] can be understood as derived from a 21-crown-7-structure. While [3.2.1] is still very three dimensional and cryptand like with three not so different bridging arms, [4.1.1] is already close to the two dimensional crown structure of the 21-crown-7 as underlined by the same ion selectivity of Cs^+.[23] Therefore, we can understand the three isomeric cryptand structures [2.2.2] via [3.2.1] to [4.1.1] as the path from three dimensional cryptands to two dimensional coronands.

Summary

By application of density functional theory, we examined the possibility of selective alkali and alkaline earth metal complexation by the unsymmetrical [3.2.1] and [4.1.1] cryptands. The smaller cavity size of the [3.2.1] cryptand is best suited for K^+ (0.41 kcal/mol) and Ba^+ (-16.03 kcal/mol) cations. The larger [4.1.1] cryptand is perfectly suited to accommodate larger metal cations Cs^+ (-2.69 kcal/mol), Ca^{2+} (-10.82 kcal/mol), Sr^{2+} (-10.93 kcal/mol) and Ba^{2+} (-10.04 kcal/mol). The different size of the O-Et-O-bridging arms of the investigated cryptands provide a great flexibility and adaptability of the host system to accommodate encapsulated metal cations. In comparison to the [2.2.2] cryptand, the [3.2.1] cryptand is better suited for K^+, Rb^+, Sr^{2+} and Ba^{2+}, whereas in the case of the [4.1.1] cryptand it would be Na^+, K^+, Sr^{2+} and Ba^{2+} cations.

Acknowledgments

**Keywords:** selective ion complexation · cryptand · DFT-study

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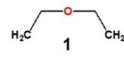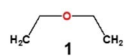[23] H. K. Frensdorff, *J. Am. Chem. Soc.* **1971**, *93*, 600–606.

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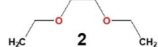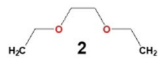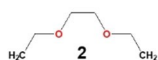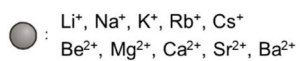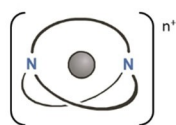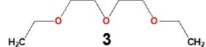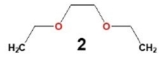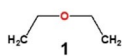
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1 – 8

[3.2.1] and [4.1.1] isomers of Lehn's [2.2.2] Cryptand: Prediction of ion selectivity by quantum chemical calculations XV