

## IIA/IIB group metal cations hosted by $\beta$ -cyclodextrin: a DFT study

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*Dedicated to Acad. Ivan Juchnovski on the occasion of his 80<sup>th</sup> birthday*

Although there is a lot of information about cyclodextrins (CDs) and their coordination complexes, there are still many open questions concerning the factors influencing the processes of their metal binding and selectivity. The purpose of this study is to clarify the factors that drive the formation of  $\beta$ CDs - metal ion complexes. A DFT computational study of complexes of  $\beta$ CDs with IIA/IIB group metal cations ( $\text{Be}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Hg}^{2+}$ ) was performed to determine the main factors (ionic radius, preferred coordination number and degree of hydration of the metal cation, dielectric constant of the medium, etc.) controlling the processes of metal binding and selectivity in these systems.

**Key words:** cyclodextrin; metal cations, metal binding; selectivity; DFT calculations

### INTRODUCTION

Some of the most commonly used molecules in the host-guest interactions are cyclodextrins (CDs). They are macromolecules which possess amphoteric properties, because they have hydrophobic cavity and hydrophilic outer surface. The natural CDs consist of 6, 7 or 8 glucopyranose units and are referred to as  $\alpha$ CD,  $\beta$ CD and  $\gamma$ CD, respectively [1]. The form of cyclodextrins is truncated cone because of the chair conformation of the glucopyranose units [2]. For industrial use CDs are manufactured by enzymatic degradation of starch [3]. All three major types naturally occurring CDs have the same side rim depth – about 0.8 nm, but they have different cavity diameters (empty diameters between anomeric oxygen atoms) - 0.5, 0.6 and 0.8 nm for  $\alpha$ CD,  $\beta$ CD and  $\gamma$ CDs, respectively [4]. Due to the large number of OH-groups CDs are soluble in water and the solubility of the  $\alpha$ CD,  $\beta$ CD and  $\gamma$ CD under normal conditions is approximately 13%, 2% and 26% (145 g/l, 18.5 g/l and 232 g/l, respectively) [5]. One of the most important properties of CDs is their ability to accommodate different molecules inside their cavity [3,6,7], as the size of molecules that can be placed inside (hosted) is determined by the CDs cavity size. As a result, these molecules have found a number of applications in a wide range of fields. In the pharmaceutical industry CDs are primarily

used as complexing agents to increase the water solubility of poorly water-soluble drugs and to increase their bioavailability and stability [2,8,9]. For example,  $\beta$ CD is used as an agent to increase the solubility and reduce the adverse side effects (gastrointestinal irritation) of the Piroxicam (belonging to the group of nonsteroidal anti-inflammatory drugs), its faster absorption and thus faster analgesic effect [10]. CDs can alter the chemical stability of drugs - may slow down or accelerate their degradation or influence their reactivity. For example, doxorubicin (an antitumor drug) is unstable in aqueous medium and complexation with  $\beta$ CD or  $\gamma$ CD significantly increases its stability [11]. CDs inclusion complexes with metals, where CD acts as a ligand from the first coordination sphere, are described in the literature. One of the most interesting examples is the complex of  $\beta$ CD with  $\text{Cu}^{2+}$ , which also include  $\text{Li}^+$  [12].  $\beta$ CD may also form complexes with metal ions in which it is in the second coordination sphere: for instance adducts of ferrocene and  $\beta$ CD, described by Breslow [13]. Zhang et al. [14] investigated complexes of  $\beta$ CD with  $\text{M}^{2+}$  ( $\text{Fe}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$  and  $\text{Zn}^{2+}$ ) and demonstrated that these complexes have catalytic properties in aldol condensation reaction. Stachowicz et al. [15] studied computationally the complexes of  $\beta$ CD with some metal cations ( $\text{Na}^+$ ,  $\text{Cu}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Al}^{3+}$ ) at the B3LYP/6-31G\* level and revealed the structure of the formed host-guest complexes.

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The aims of the present study are: (a) to clarify whether the properties of the metal ion influence the process of metal -  $\beta$ CD complexation; (b) to verify how dielectric properties of the medium affect the process of metal binding and the selectivity in these complexes; (c) to check which type of coordination mode of  $\beta$ CD (as first or second coordination sphere) is more favorable. In achieving these aims, we conducted DFT calculations combined with the PCM computations (Polarizable Continuum Model) for the complexes of  $\beta$ CD with IIA/IIB group metal ions.

### COMPUTATIONAL DETAILS

All calculations in this work were performed by using Gaussian 09 quantum chemistry package [16]. For geometry optimization of the  $\beta$ CD molecule and its complexes with metal ions M062X functional was employed [17]. The computations were performed with the 6-31G(d,p) basis set [18] for the lighter atoms (C, O, H, Be, Mg, Ca, Zn) and with SDD pseudopotential [19,20] for Sr, Ba, Cd and Hg. In our previous study this combination of functional and basis set (M062X/6-31G(d,p)) has been proven to reproduce accurately metal–oxygen atoms distances in a metal complex with ligand resembling CD molecule [21]. For each optimized structure frequency calculations were performed at the same level of theory. No imaginary frequency was found for the lowest energy configurations of any of the optimized structures. The scaled by an empirical factor of 0.979 vibrational frequencies were used to compute the thermal energies,  $E_{th}$ , including zero-point energy, and entropies,  $S$ . The free energy of complex formation in the gas phase at  $T=298.15$  K,  $\Delta G^1$ , was calculated by equation (1):

$$\Delta G^1 = \Delta E_{el} + \Delta E_{th} + \Delta PV - T\Delta S \quad (1)$$

where the terms  $\Delta E_{el}$ ,  $\Delta E_{th}$  and  $\Delta S$  are differences between the respective values of energies of the products and reactants, and the term  $\Delta PV$  is a work term.

Solvation effects were accounted for by employing the Polarizable Continuum Model (PCM) [22,23] method. The fully optimized structure of each molecule/complex in the gas phase was subjected to a single point calculation in water ( $\epsilon \approx 80$ ). The free energy of the complex formation in water was obtained by equation (2), where  $\Delta G_{solv}^{80}$  (Products) and  $\Delta G_{solv}^{80}$  (Reactants) are differences between the gas-phase and PCM calculated energies for the products (complexes) and reactants ( $\beta$ CD and metal cations), respectively:

$$\Delta G^{80} = \Delta G^1 + \Delta G_{solv}^{80}(\text{Prod.}) - \Delta G_{solv}^{80}(\text{React.}) \quad (2)$$

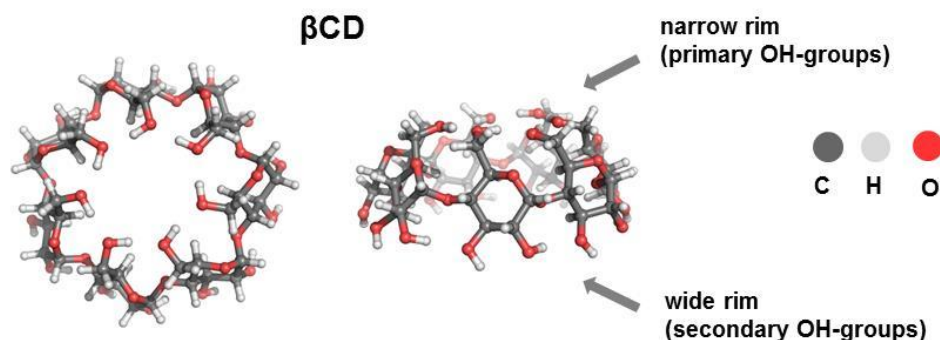
The calculated values of  $\Delta G^{80}$  can be positive or negative: if the obtained value is positive, then the complex formation is thermodynamically unfavorable; if  $\Delta G^{80}$  value is negative, then the process is thermodynamically favorable.

The PyMOL molecular graphics system was used for generating the molecular graphics images [24].

### RESULTS AND DISCUSSION

#### $\beta$ CD

Figure 1 presents the lowest-energy optimized structure of  $\beta$ CD in two projections – a view from the narrow rim and a side view. The  $\beta$ CD system possesses nearly 7-fold symmetry with main symmetry z-axis passing through the centre of the  $\beta$ CD and perpendicular to the mean plane of the oxygen atoms from the primary OH groups. Hydrogen bonds are formed at the trimmed with OH groups rims (upper/narrow and lower/wide rim); these at the narrow rim are stronger than their wide-rim counterparts.



**Fig. 1.** Optimized structure of  $\beta$ CD in two projections: side view and view from the narrow rim.

The orientation of intramolecular hydrogen bonds at both rims is opposite: looking from the narrow rim side the orientation of the narrow rim hydrogen bonds is counter-clockwise, while the wide rim hydrogen bonds is clockwise.

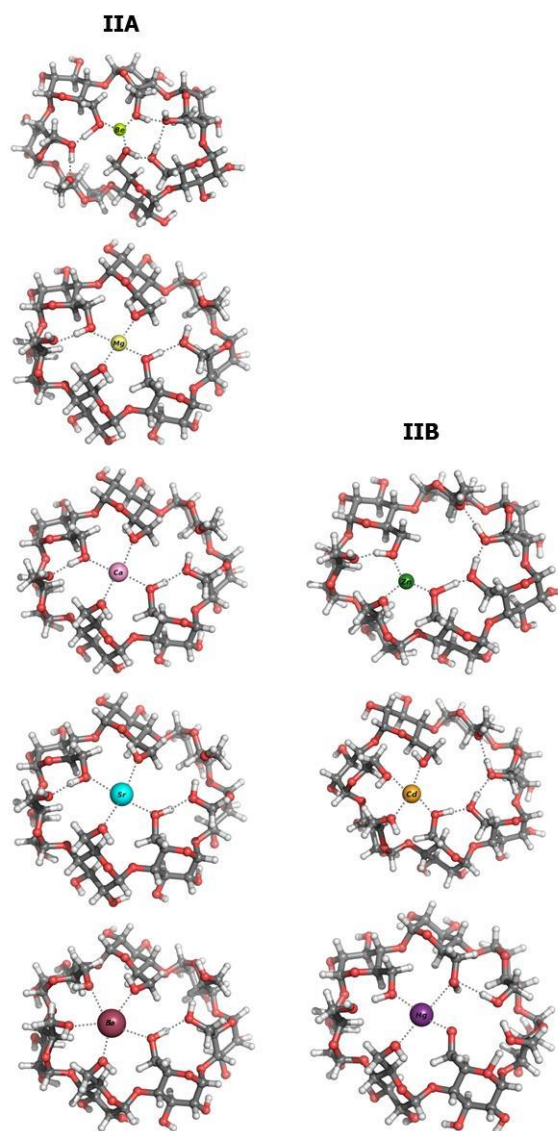
*$\beta$ CD as a first-shell ligand for IIA/IIB group metal cations:  $[\beta\text{CD}-\text{M}]^{2+}$  complexes*

Formation of  $[\beta\text{CD}-\text{M}]^{2+}$  complexes (M = IIA/IIB group metal) where  $\beta$ CD acts as a first-shell ligand to the metal cation, was studied. The optimization of the  $[\beta\text{CD}-\text{M}]^{2+}$  structures was initiated from geometry with the preferred metal cation positioning- at the center of the narrow rim plane of the optimized structure of the free  $\beta$ CD. The optimized structures of the resultant metal complexes are shown in Figure 2. The initial shape of truncated cone becomes distorted for all metal cations. The mode of metal binding to the host cyclodextrin depends on the ionic radius of the guest cation: bulkier cations tend to coordinate to larger number of hydroxyl groups from the narrow rim while smaller cations prefer smaller number of binding partners, so the final geometries of the  $[\beta\text{CD}-\text{M}]^{2+}$  complexes differ.  $\text{Be}^{2+}$  and  $\text{Zn}^{2+}$  are three-coordinated having only three adjacent hydroxyl partners,  $\text{Ba}^{2+}$  exhibit coordination number of 5 in the complex, while the rest of the cations have coordination number of 4. The  $\text{M}-\text{O}_{\beta\text{CD}}$  distances, ionic radii of metal cations and free energies of complex formation in the gas-phase and water environment are presented in Table 1.

**Table 1.**  $\text{M}-\text{O}_{\beta\text{CD}}$  distances (Å), ionic radii of metal cations (Å) and Gibbs free energies (in kcal/mol) in the gas phase (superscript 1) and water environment (superscript 80) calculated for the metal complex formation reaction,  $\beta\text{CD} + \text{M}^{2+} \rightarrow [\beta\text{CD}-\text{M}]^{2+}$

Metal cation	$\text{M}-\text{O}_{\beta\text{CD}}$	ionic radius <sup>a</sup>	$\Delta G^1$	$\Delta G^{80}$
$\text{Be}^{2+}$	1.56	0.27	-439.9	-116.6
$\text{Mg}^{2+}$	2.02	0.72	-300.7	-31.8
$\text{Ca}^{2+}$	2.34	1.00	-219.9	-4.5
$\text{Sr}^{2+}$	2.46	1.18	-179.7	13.6
$\text{Ba}^{2+}$	2.73	1.35	-155.8	32.7
$\text{Zn}^{2+}$	2.64	0.74	-331.9	-24.0
$\text{Cd}^{2+}$	2.30	0.95	-259.0	29.5
$\text{Hg}^{2+}$	2.40	1.02	-273.3	54.2

<sup>a</sup>Ionic radius in tetracoordinated  $\text{Be}^{2+}$  complexes and hexacoordinated complexes for the rest of the dications; from Shannon, 1976 [25].



**Fig. 2.** M062X/6-31G(d,p) fully optimized structures of  $[\beta\text{CD}-\text{M}]^{2+}$  complexes in the gas phase.

As the data in Table 1 reveal, the smaller the cationic radius (and higher the respective charge density of the cation) the more thermodynamically favorable is the complex formation in the respective subgroup (lower free energy values for the smaller cations than their bulkier counterparts in each subgroup). The results obtained demonstrate that all the reactions in the gas phase are favorable characterized with quite large negative formation free energies  $\Delta G^1$ . Solvation effects, however, significantly attenuate the free energy gains in the gas phase and render some reactions unfavorable in aqueous solution (positive  $\Delta G^{80}$  values for the  $\text{Sr}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Cd}^{2+}$  and  $\text{Hg}^{2+}$  complex formation). In comparing the magnitude of  $\Delta G^1$  and  $\Delta G^{80}$  between IIA and IIB subgroups, the role of charge-accepting ability of the guest cation in complex formation

stands out. Cations from the B subgroup are better electron density acceptors than their counterparts from the A subgroup with similar ionic radii due to favorable hybridization between the valence s-orbital and highest occupied d-orbitals resulting in low-lying electron-receptive orbitals. For example, between  $\text{Zn}^{2+}$  and  $\text{Mg}^{2+}$ , two cations with virtually identical ionic radii (0.74 and 0.72 Å, respectively), the complex of the former is more stable in the gas phase characterized by lower  $\Delta G^1$  value than that of the latter. The same trend is observed for  $\text{Cd}^{2+}$  and  $\text{Ca}^{2+}$ , and  $\text{Hg}^{2+}$  and  $\text{Sr}^{2+}$  in the gas phase ( $\Delta G^1$  values). The series of cations with similar ionic radii ( $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Sr}^{2+}$  vs.  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Hg}^{2+}$ ) show the opposite trend in  $\Delta G^{80}$  values. The explanation lies in the difference in the desolvation penalties for these metal cations.

*$\beta$ CD as a ligand for monohydrated IIA/IIB group metal cations:  $[\beta\text{CD}-\text{M}-\text{H}_2\text{O}]^{2+}$  complexes*

The effect of metal hydration on complexation process was studied by employing supramolecular approach. Formation of  $[\beta\text{CD}-\text{M}-\text{H}_2\text{O}]^{2+}$ , where  $\beta\text{CD}$  acts as a ligand to monohydrated  $[\text{M}-\text{H}_2\text{O}]^{2+}$  metal cation (Figure 3), was studied. The  $\text{M}-\text{O}_{\beta\text{CD}}$  and  $\text{M}-\text{O}_{\text{H}_2\text{O}}$  distances, ionic radii of metal cations and free energies of complex formation are listed in Table 2. The addition of one water molecule affects slightly the distances  $\text{M}-\text{O}_{\beta\text{CD}}$ , and almost all of them (except for the zinc complex) slightly increase (0.02 ÷ 0.08 Å).  $\text{M}-\text{O}_{\text{H}_2\text{O}}$  distances have similar values to the respective  $\text{M}-\text{O}_{\beta\text{CD}}$  ones. The dependence of  $\Delta G^1$  on the ionic radius is the same as in the complexes without added  $\text{H}_2\text{O}$  molecule, but  $\Delta G^1$  values here fall in a narrow range (the lowest value is  $-320.6 \text{ kcal mol}^{-1}$ , and the highest is  $-131.4 \text{ kcal mol}^{-1}$ ).

**Table 2.**  $\text{M}-\text{O}_{\beta\text{CD}}$  and  $\text{M}-\text{O}_{\text{H}_2\text{O}}$  distances (Å), ionic radii of metal cations (Å) and Gibbs free energies (in kcal/mol) in the gas phase (superscript 1) and water environment (superscript 80) calculated for the monohydrated metal complex formation reaction,  $\beta\text{CD} + [\text{M}-\text{H}_2\text{O}]^{2+} \rightarrow [\beta\text{CD}-\text{M}-\text{H}_2\text{O}]^{2+}$ .

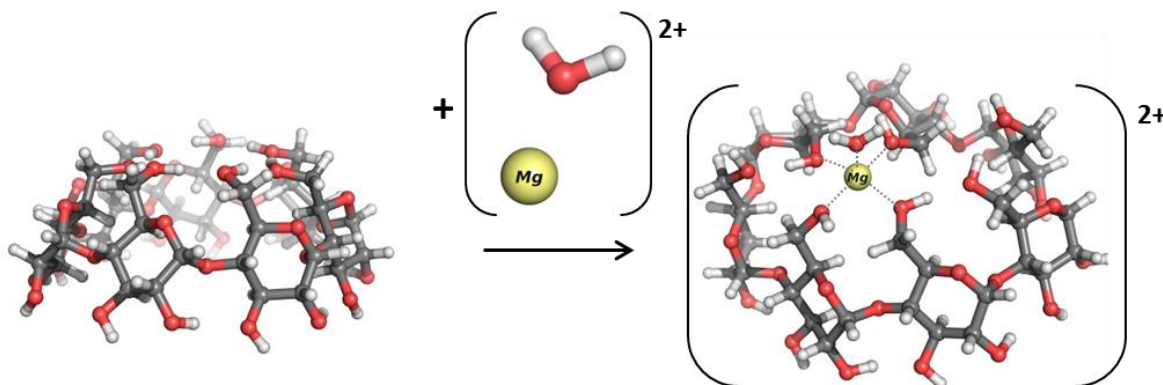
Metal cation	$\text{M}-\text{O}_{\beta\text{CD}}$	$\text{M}-\text{O}_{\text{H}_2\text{O}}$	ionic radius <sup>a</sup>	$\Delta G^1$	$\Delta G^{80}$
$\text{Be}^{2+}$	1.63	1.68	0.27	-320.6	-100.8
$\text{Mg}^{2+}$	2.05	2.04	0.72	-244.6	-32.0
$\text{Ca}^{2+}$	2.36	2.37	1.00	-189.0	-5.3
$\text{Sr}^{2+}$	2.49	2.49	1.18	-151.2	14.0
$\text{Ba}^{2+}$	2.76	2.64	1.35	-131.4	28.5
$\text{Zn}^{2+}$	1.96	2.04	0.74	-252.7	-26.6
$\text{Cd}^{2+}$	2.29	2.29	0.95	-199.3	179.3
$\text{Hg}^{2+}$	2.42	2.54	1.02	-195.6	51.7

<sup>a</sup>Ionic radius in tetracoordinated  $\text{Be}^{2+}$  complexes and hexacoordinated complexes for the rest of the dications; from Shannon, 1976 [25].

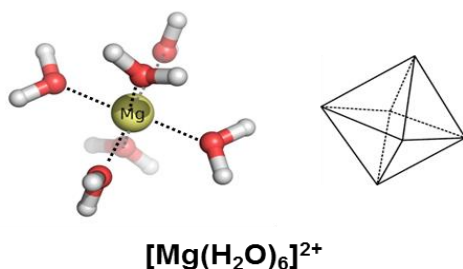
Four positive  $\Delta G^{80}$  values are observed, i.e. the water molecule addition does not render complex formation with  $\text{Sr}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Cd}^{2+}$  and  $\text{Hg}^{2+}$  favorable.

*$\beta$ CD as a ligand for hexahydrated IIA/IIB group metal cations:  $[\beta\text{CD}-\text{M}(\text{H}_2\text{O})_6]^{2+}$  complexes*

The group II metals in their +2 oxidation state have a hydration number of 6 (except  $\text{Be}^{2+}$ ) with octahedral arrangement of the water ligands (Figure 4). Magnesium hexaaqua complex,  $[\text{Mg}(\text{H}_2\text{O})_6]^{2+}$ , was modeled as a representative of the hydrated metal species from the series and taken for further evaluations.



**Fig. 3.**  $[\beta\text{CD}-\text{Mg}-\text{H}_2\text{O}]^{2+}$  complex formation reaction.



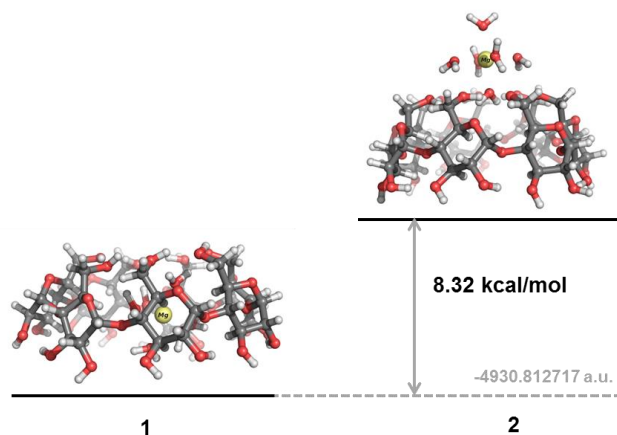
**Fig. 4.** Magnesium hexaaqua complex  $[\text{Mg}(\text{H}_2\text{O})_6]^{2+}$ ;  $\text{M}-\text{O}_{\text{H}_2\text{O}} = 2.06 \text{ \AA}$

Two complexes of hexaaqua magnesium ion with  $\beta\text{CD}$  were modeled and the metal binding affinities of different localities of the host cavity were probed:

(1)  $[\text{Mg}(\text{H}_2\text{O})_6]^{2+}$  complex is entirely buried inside the cavity;

(2)  $[\text{Mg}(\text{H}_2\text{O})_6]^{2+}$  ion is located outside the cavity, near the narrow rim of the  $\beta\text{CD}$ , and only one of the water molecules is located inside the cavity of the  $\beta\text{CD}$ .

The overall shapes of the discussed complexes, as well as their relative stability are shown in Figure 5 and Table 3. As the calculations reveal, the structure where the  $[\text{Mg}(\text{H}_2\text{O})_6]^{2+}$  ion is placed inside the cavity of the  $\beta\text{CD}$  is more stable and advantageous in the gas phase.



**Fig. 5.** Optimized structures and relative stabilities of the  $[\beta\text{CD}-\text{Mg}(\text{H}_2\text{O})_6]^{2+}$  complexes.

**Table 3.** Calculated Gibbs free energies in the gas phase ( $\Delta G^1$ ) and in water environment ( $\Delta G^{80}$ ) (in  $\text{kcal mol}^{-1}$ ) for  $[\beta\text{CD}-\text{Mg}(\text{H}_2\text{O})_6]^{2+}$  complex formation,  $\beta\text{CD} + [\text{Mg}(\text{H}_2\text{O})_6]^{2+} \rightarrow [\beta\text{CD}-\text{Mg}(\text{H}_2\text{O})_6]^{2+}$

Complex	$\Delta G^1$	$\Delta G^{80}$
1	-84.79	-10.31
2	-76.47	-12.76

Note that the metal binding to the host molecule in both locations is favorable as evidenced by the negative values of  $\Delta G^1$  and  $\Delta G^{80}$  in Table 3, but the interaction free energies are less negative than those of the respective host-(bare-guest) complexation (Table 1).

## CONCLUSION

The presented results confirm that the complex formation process between IIA and IIB group metal cations and  $\beta\text{CD}$  is thermodynamically favorable. Coordination of hydrated metal ions into the hydrophobic cavity of the  $\beta\text{CD}$  is also possible, with pronounced preference for metals with small ionic radii. Complexation free energies are strongly affected by the dielectric properties of the medium: increasing the dielectric constant of the surroundings attenuates the free energy gains on complexation. Regardless of whether the metal ion is hydrated or not, the most advantageous position in the cavity is close to the narrow rim of the cyclodextrin, where the negative charge is concentrated.

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## КОМПЛЕКСООБРАЗУВАНЕ МЕЖДУ МЕТАЛНИ ЙОНИ ОТ ПА/ІВ ГРУПИ И β-ЦИКЛОДЕКСТРИН: ИЗСЛЕДВАНЕ С ТЕОРИЯ НА ФУНКЦИОНАЛА НА ПЛЪТНОСТТА

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(Резюме)

Въпреки че има много информация за циклодекстрините и техните координационни комплекси, все още много въпроси, свързани с факторите, определящи процесите на тяхното метално свързване и селективност остават неизяснени. Целта на това изследване е да се уточнят факторите, ръководещи формирането на комплекси на β-циклодекстрин и метални йони. Проведено е изследване на комплекси на β-циклодекстрин с метални йони от ПА/ІВ група ( $\text{Be}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Hg}^{2+}$ ) с използване на метода на Теория на Функционала на Плътността (ТФП). Определени са основните фактори (йонен радиус, предпочитано координационно число, степен на хидратация на металния катион и диелектрична константа на средата), които контролират процесите на метално свързване и селективност в тези системи.