Metal-ligand bonding in bispidine chelate complexes for radiopharmaceutical applications

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Abstract

The complexes of selected radionuclides relevant for nuclear medicine (In^{III} , Bi^{III} , Lu^{III} , Ac^{III} and in addition La^{III} for comparative purposes) with the octadentate (6,6'-((9-hydroxy-1,5-bis(methoxycarbonyl)-2,4-di(pyridin-2-yl)-3,7-diazabicyclo[3.3.1]nonane-3,7-diyl)bis(methylene))dipicolinic acid) ligand, H_2bispa^2 , have been studied by density functional theory calculations modelling both isolated and aqueous solution conditions. The properties in focus are the encapsulation efficiency of the ligand for the different-size metals (M), the differences in bonding with the various M^{III} ions analysed using Bader's atoms in molecules theory and the possibility and characteristics of nona- and decacoordination by H_2O ligands. The computed results confirmed strong steric effects in the case of the In complex excluding higher than octacoordination. The studied properties depend strongly on the interplay of the sizes and electronic structures of the M^{III} ions. The computations support high stability of the complexes in aqueous solution, where also the solvation energies of the M^{III} ions (as dissociation products) play a significant role.

Keywords Radiopharmaceuticals · Bispa · Water addition · Coordination number · Bonding · Thermodynamic stability

Introduction

Radioisotopes are very efficient in treating cancer and other cases of abnormal tissue growth [1, 2]. The method is based on ionizing radiation, which can break DNA molecules, preventing in this way their replication. In order to avoid a large-scale destruction of healthy tissues, the radiopharmaceuticals should be transferred directly to the diseased cells. For the same reason, preferably α -emitting radioisotopes should be applied utilizing the short range of this radiation. The technique is called targeted- α -therapy (TAT) and has only recently been introduced in clinical applications [2–11]. Accordingly, the field is still subjected to extensive research. A major issue is to find the most optimal transport agents for the various radioisotopes relevant for TAT. These transport agents are biological targeting vectors (antibody or peptides that have affinity for cancer cells) containing the

radionuclide in chelated form [12]. The chelating agent has a key role in the process: an efficient transport requires highly stable chelate complexes with both the radiopharmaceuticals and the (generally also radioactive) decay products to be departed from the body.

Bispidine ligands represent very promising chelating agents for radiopharmaceutical applications [13–15]. The rigid bispidine scaffold can be extended by a variety of donor sets using relatively simple synthetic routes. Ligands with coordination numbers ranging from 4 to 8 containing O and N donors have been reported [14–16]. Variation of the pendant groups resulted in specific bispidine ligands for a range of radiometal ions, showing high complex stability, inertness and fast complexation kinetics [14, 16]. An additional advantage for medical applications is their simple conjugation to peptides or antibodies [17–21].

The excellent complexation properties of bispidines are due to the rigid diazaadamantyl backbone containing two preorganized tertiary amines and two pendant pyridine donors. Additional multidentate pendant groups can be attached to the tertiary amines facilitating efficient encapsulation of specific metal ions in their preferred coordination geometry [14, 22]. This is achieved by the pendant groups creating an elastic coordination sphere, where the

Dedicated to the memory of Richard F. W. Bader (1931–2012)!

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metal ions can accomplish their preferred coordination numbers. The highly preorganized open-chain ligands can also facilitate fast complex formation.

Earlier radiopharmaceutical studies of bispidines have focussed on encapsulating Cu^{II} ($^{64/67}\text{Cu}^{\text{II}}$ being a PET tracer) by penta- and hexadentate ligand systems [17, 23–27]. Recently, the octadentate bispa derivative, H_2bispa^2 (6,6'-((9-hydroxy-1,5-bis(methoxycarbonyl)-2,4-di(pyridin-2-yl)-3,7-diazabicyclo[3.3.1]nonane-3,7-diyl) bis(methylene))dipicolinic acid) has been probed for larger radionuclides relevant for nuclear medicine (In^{III} , Bi^{III} , Lu^{III} and La^{III} as surrogate for $^{225}\text{Ac}^{\text{III}}$) [16, 28]. The latter experimental studies revealed high stabilities of the metal complexes and fast complex formation under ambient conditions. In addition, two isomeric picolinate-/acetate-based heptadentate bispa derivative ligands also showed very efficient complexation kinetics with Bi^{III} at ambient temperature and kinetic stabilities comparable with those of standard ligands used in the field [28].

The present theoretical study aims to uncover the bonding characteristics of the H_2bispa^2 ligand with therapeutically relevant In^{III} , Bi^{III} , Lu^{III} and Ac^{III} cations (Fig. 1). In order to assess the effect of different electronic structures of lanthanides and main group metals, the complexes of La^{III} and Bi^{III} (having nearly the same ionic radii) are compared. The main questions include the encapsulation efficiency of the ligand for the different-size metals, the differences in bonding formed by the various metal ions and the effects of H_2O -coordination.

Computational details

The density functional theory (DFT) computations were carried out with the Gaussian 09 suit of programs [29]. On the basis of the reported good performance of the TPSSh meta-hybrid functional [30] for the molecular geometries and relative stabilities of various complexes [31–35], this functional was applied throughout the present study. The grid specification for the two-electron integrals was 150 radial shells and 974 angular points per shell (150,974; SuperFineGrid keyword) for H, C, N and O and (225,974) for the heavier elements. For the self-consistent field (SCF) convergence, Tight criteria have been used corresponding to $1.00\text{E}-08$ in convergence on the RMS density matrix and $1.00\text{E}-06$ in energy change. The basis sets were selected on the basis of test calculations on the $\text{In}(\text{bispa}^2)^+$ complex compared with the crystal structure of $[\text{In}(\text{bispa}^2)]$ [TFA] [16]. In the benchmark calculations for In, the large-core (LC) ECP46MWB [36] and small-core (SC) ECP-28MDF [37] pseudopotentials in conjunction with valence basis sets of contraction schemes (4s4p)/(2s2p) [36] and cc-pVDZ (8s6p6d)/(4s3p2d) or cc-pVTZ (12s11p9d1f)/(5s4p3d1f) [38], respectively, were utilized. For the light atoms, the standard 6-31G(d,p) and 6-311G(d,p) bases extended eventually with diffuse functions on N and O were probed. The dispersion effects were considered using the empirical D3 parameters of Grimme et al. with the original D3 damping function [39] as well as with Becke-Johnson damping (D3BJ) [40].

Fig. 1 **a** The H_2bispa^2 ligand with numbering of the most relevant moieties; **b** structure of the $\text{Bi}(\text{bispa}^2)^+$ complex (Bi, violet; carbon, grey; oxygen, red; nitrogen, blue; hydrogens of bispa^2 are removed for better visibility). The structure is gradually fainter towards the back

The performance of each probed computational level is assessed by comparing the X-ray diffraction and computed In-ligand distances in Table S1 of the Supplementary Information. The general feature of all tested levels is the underestimation of the M-O, and overestimation of the M-N distances with respect to the solid-phase data. Such deviations are understandable in view of the missing intermolecular interactions in the computed isolated molecules. Under the latter conditions, the strongly anionic carboxylate oxygens focus on the interaction with the metal ions and thus the overestimated M-O bonds pull the metal away from the N donors.

On the basis of the above benchmark calculations, the SC pseudopotential was selected for the metals in conjunction with the 6-311(+)G(d,p) basis for the light atoms and the D3BJ dispersion correction. For the metals, this means the following pseudopotentials and valence basis sets: ECP60MDF + cc-pVTZ with (12s11p8d1f)/(5s4p3d1f) contraction for Bi [37, 38] and ECP-28MWB + (14s13p10d8f6g)/(10s8p5d4f3g) valence basis for La and Lu [41, 42]. Unfortunately, severe SCF convergence problems occurred with the SC pseudopotential (ECP-60MWB + (14s13p10d8f6g/10s9p5d4f3g) valence basis) of Ac [43, 44]; therefore, for this metal, the large-core ECP-78MWB pseudopotential with the contracted (7s6p5d2f1g)/(6s5p4d2f1g) valence basis [45] set was used. In a recent study on Ac(macropa) complexes including both the SC and LC pseudopotentials for Ac [34], differences in the magnitude of 0.01 Å in the metal-ligand distances and 50 kJ/mol in the dissociation energies were observed comparing the results obtained by the two Ac pseudopotentials. All the applied pseudopotentials here cover the scalar relativistic effects, which are particularly important for the heavy metals.

The geometries of all the studied complexes were optimized at the above levels of theory using default convergence criteria to a maximum step size of 0.0018 au and a maximum force of 0.00045 au. The minimum characters were confirmed by frequency calculations. For the free (bispa²)²⁻ ligand molecule, five conformations (selected by steric considerations) were optimized and the lowest-energy one was used in the evaluation of dissociation energies. The Cartesian coordinates of the optimized structures are given in the Supplementary Information. The quantum theory of atoms in molecules (QTAIM [46–48]) analysis was performed with the Multiwfn code using a medium-quality grid [49].

Dissociation energies were corrected for basis set superposition error (BSSE) using the counterpoise method [50]. The solvent effects were taken into account using the polarizable continuum model (PCM) [51, 52] with radii and non-electrostatic terms from the SMD solvation model by Marenich et al. [53]. For La³⁺, Lu³⁺ and Ac³⁺, the PCM radii from literature were used (1.874 Å, 1.659 Å [31] and

1.933 Å [34], respectively). For In³⁺ and Bi³⁺, no such radii are available; therefore, they were developed in the present study (1.507 Å and 1.723 Å, respectively) on the basis of literature hydration free energies [54]. No scaling factor ($\alpha = 1.0$) was applied for the PCM radii in the present study. The solvation energies were evaluated in single-point calculations on the optimized geometries of the isolated molecules. Recently, a similar theoretical model reproduced excellently the experimental stability relations of lanthanide complexes [31].

In order to account for the reduction of the translation entropy of water molecules in aqueous solution, the water pressure was set to 1354 atm (value derived from the liquid water density of 997.02 kg/m³ at 298 K) instead of 1 atm [55, 56] in the calculation of its Gibbs free energy.

Structural characteristics

The bispa² anionic ligand captures well the present metal ions in its cavity by means of eight coordinative metal-ligand bonds. (Unlike - in the past well-studied - Cu^{II} [17, 23–27], the sizes of the present metal ions are large enough for octa-coordination.) The ligand coordination is achieved by the two deprotonated picolate oxygens and the six nitrogens of bispa² (cf. Fig. 1b). Accordingly, the isolated complex molecule without counterion has a single positive charge, M(bispa²)⁺.

As the donor–acceptor distances in Fig. 2 indicate, the strongest metal-ligand interaction is generally achieved with the anionic picolate oxygens. In the case of the In complex (with the shortest M^{III} ionic radius), the M-O_{pic} and M-N_{pic} (N₁, N₂; cf. Fig. 1a) distances are comparable, while in the other M(bispa²)⁺ complexes, the M-O_{pic} distances are considerably smaller than the M-N_{pic} ones. In fact, the coordination of N_{pic} loses its importance with the larger metal ions, shown by the difference between M-O_{pic} and M-N_{pic} increasing in a larger extent than the M^{III} size. In the La and Ac complexes, the M-N_{pic} bonds weaken almost to the level of the other nitrogens. In the case of In(bispa²)⁺, the M-O_{pic} distances are larger than expected from the trend in the M^{III} ionic radii [57]. The spatial requirements of the small In^{III} ionic radius supported by the propensity of In^{III} for short-range covalent interactions are mainly responsible for this compact arrangement of the picolate groups. The more relaxed conditions in the other complexes allow the orientation of the picolate groups guided by the anionic O_{pic} atoms. Another indication of the strong steric effects in the compact In(bispa²)⁺ molecule is that the pyridine ring with N₄ is crowded out from the close vicinity of In. The declination of this pyridine ring is somewhat larger in the crystal, where additional effects like crystal packing and intermolecular interactions are also possible.

Fig. 2 Metal-ligand bond distances in the $M(\text{bispa}^2)^+$ complexes compared to the M^{III} effective ionic radii for 6- and 8-coordination ($\text{\AA}$) [57]. For the numbering of atoms, see Fig. 1a. The presented values are given in Table S2 of the Supplementary Information

Comparing the trends across M in Fig. 2, the best agreement with the M^{III} ionic radii can be observed for the weakest interactions with the bispidine nitrogens (N_5 , N_6). $M-N_3$ and $M-N_1/N_2$ (increasing in a nearly straight line from In to Ac) do not seem to be sensitive to the small variations in the M^{III} ionic radii. It should be noted that though the ionic radii of Bi^{III} and La^{III} are nearly the same, most of the presented distances suggest a stronger bonding of Bi. This can be explained by the different bonding in the p-block (Bi) and f-block (La) elements. The main differences include the generally larger electronegativities of the p-block elements, hence a larger propensity for covalent bonding established by the valence p orbitals in contrast to the more ionic lanthanides.

Saturation of the first coordination sphere with H_2O molecules

In the case of large captured metal ions, a coordinatively unsaturated space is available between the picolinate and pyridine groups (on the top side of Fig. 1b), where small molecules could additionally coordinate. Direct coordination of an NO_3^- ion to Bi^{III} has been found in the crystal of $[\text{Bi}(\text{bispa}^2)(\text{NO}_3)] \cdot \text{H}_2\text{O}$, while a replacement of NO_3^- ions by solvent molecules in solution was consistent with NMR data [28]. Beyond this observed nonadentate coordination, the possibility of decadentate coordination was postulated by Bruchertseifer et al. [28]. The coordination of H_2O at the

molecular level was probed in the present study by optimizing the $M(\text{bispa}^2)(\text{H}_2\text{O})^+$ and $M(\text{bispa}^2)(\text{H}_2\text{O})_2^+$ complexes for the five M^{III} ions. The obtained characteristic structures of the nona- and decadentate complexes are shown in Fig. 3.

Both mono- and bicoordination of H_2O were obtained for the present M^{III} ions except for In^{III} . The bispa^2 ligand surrounds this latter small ion completely and does not leave sufficient space for coordination of H_2O . The starting $\text{In}(\text{bispa}^2)(\text{H}_2\text{O})^+$ and $\text{In}(\text{bispa}^2)(\text{H}_2\text{O})_2^+$ structures derived from the $\text{Lu}(\text{bispa}^2)(\text{H}_2\text{O})^+$ and $\text{Lu}(\text{bispa}^2)(\text{H}_2\text{O})_2^+$ ones changed upon geometry optimization to $\text{In}(\text{bispa}^2)^+$ with the H_2O ligands moving into the second coordination sphere and hydrogen-bonded to the picolinate oxygens.

The lack of (even one) H_2O -coordination to $\text{In}(\text{bispa}^2)^+$ seems to be strange in the view of the 8-coordinate In^{III} ionic radius being smaller only by $0.06 \text{ \AA}$ than that of Lu^{III} . In order to understand this significant difference between $\text{In}(\text{bispa}^2)^+$ and the other complexes, the cavities around the picolinate arms need to be analysed in detail.

There are two small cavities of similar size in this space section defined by the heteroatoms $\text{O}_1, \text{N}_2, \text{N}_4$ and $\text{O}_2, \text{N}_1, \text{N}_3$, respectively. The two cavities are separated by the $\text{M}-\text{O}_1$ and $\text{M}-\text{O}_2$ bonds. They are the strongest coordinative interactions (due to these anionic oxygens) in the bispa^2 complexes, and consequently quite rigid. Due to that, the cavities are essentially independent from each other. Coordination of additional ligands at these sites is restricted by the sizes of these independent cavities. One cavity cannot gain space for the cost of the other, and they cannot merge to a single large cavity either (without breaking of the $\text{M}-\text{O}$ bonds). Hence,

Fig. 3 Structure of the **a** $\text{Bi}(\text{bispa}^2)(\text{H}_2\text{O})^+$ and **b** $\text{Bi}(\text{bispa}^2)(\text{H}_2\text{O})_2^+$ complexes (Bi, violet; carbon, grey; oxygen, red; nitrogen, blue; hydrogen, white; hydrogens of bispa^2 are removed for better visibility). The structure is gradually fainter towards the back

if the cavity is too small for coordinating H_2O , a monocoordination is not possible either.

The sizes of these cavities are best characterized by the $\text{O}_1\text{--N}_2$ and $\text{O}_2\text{--N}_1$ distances. These heteroatoms have the shortest inter-heteroatom distances as well as the shortest coordinative bonds to the central metal ion. The coordinating H_2O ligand is in their vicinity (cf. Fig. 4); hence, its contact to them is of paramount importance. In the $\text{Lu}(\text{bispa}^2)(\text{H}_2\text{O})_2^+$ complex, the $(\text{H}_2)\text{O}\cdots\text{O}_{\text{pic}}$ and $(\text{H}_2)\text{O}\cdots\text{N}_{\text{pic}}$ non-bonding distances are around 2.46 and 2.71 Å, respectively. This facilitates $\text{Lu}\text{--O}(\text{H}_2)$ bonding distances of around 2.57 Å. The steric interactions would require similar $(\text{H}_2)\text{O}\cdots\text{O}_{\text{pic}}$ and $(\text{H}_2)\text{O}\cdots\text{N}_{\text{pic}}$ non-bonding distances in the $\text{In}(\text{bispa}^2)(\text{H}_2\text{O})^+$ complex too. Due to the proximity of picoline O and N atoms in the more compact $\text{In}(\text{bispa}^2)^+$ complex, however, these steric interactions force the H_2O oxygen to a very large distance from In^{III} (in the present theoretical model to around 3.8 Å), being too far for a coordinative bonding with the small In^{III} ion.

The $\text{M}^{\text{III}}\text{--O}(\text{H}_2)$ coordinative distances are compiled together with the $\text{O}\cdots\text{N}$ inter-picoline distances in Fig. 5. The steep increase of the latter parameter from In towards the larger metals can justify the found H_2O -coordination to $\text{Lu}(\text{bispa}^2)^+$ in contrast to $\text{In}(\text{bispa}^2)^+$. The relaxed surroundings with increasing cavities can be followed in the $\text{M}\text{--O}(\text{H}_2)$ distances. While in the case of $\text{Lu}(\text{bispa}^2)(\text{H}_2\text{O})_2^+$ the H_2O ligand coordinating in the smaller cavity

has an $\text{M}\text{--O}(\text{H}_2)$ distance larger by 0.15 Å than that in the larger cavity, in the Ac and La complexes the two $\text{M}\text{--O}(\text{H}_2)$ distances are practically the same and agree also

Fig. 4 Perspective view of the cavity defined by the $\text{O}_2, \text{N}_1, \text{N}_4$ heteroatoms in the $\text{Bi}(\text{bispa}^2)^+$ complex. The structure is gradually fainter towards the back

Fig. 5 $O_1 \dots N_2$ and $O_2 \dots N_1$ inter-picoline distances in the H_2O -free complexes and $M-O(H_2)$ distances in the $M(bispa^2)(H_2O)_x^+$ ($x = 1, 2$) complexes (Å). The presented values are given in Table S2 of the Supplementary Information

with that in the mono- H_2O complex. The large cavity of $Ac(bispa^2)^+$ was probed for a third H_2O -coordination, but this extra H_2O moved to the second coordination sphere upon geometry optimization.

The metal-ligand bond distances of the $M(bispa^2)(H_2O)_x^+$ ($x = 0-2$) complexes are compiled in Table S2 while selected ones are given in Fig. S1 of the Supplementary Information. The distance of the H_2O ligands from M falls in the magnitude of the $M-N_{pic,py}$ distances. From the two cavities of $bispa^2$, the one including N_5 is smaller, hence sterically less advantageous. Accordingly, the H_2O ligand coordinates here with a larger $M-O(H_2)$ distance. Due to this steric effect, from the two mono- H_2O isomers the one with H_2O -coordination in the larger cavity is preferred.

As a general steric effect of the H_2O -coordination, the metal- $bispa^2$ bonds are somewhat increased (empty symbols in Fig. S1). The increase is most pronounced in the Lu complex with the smallest relevant M^{III} ionic radius.

Bonding on the basis of QTAIM analysis

The electrostatic and covalent contributions to the metal-ligand interactions in the $M(bispa^2)(H_2O)_x^+$ ($x = 0-2$) complexes are assessed on the basis of the Bader atomic charges and delocalization indices, evaluated using the quantum theory of atoms in molecules (QTAIM [46–48]). The Bader charges of M and O_1 are given in Table 1; additional data are given in Table S3 of the Supplementary Information. These atoms (including the other analogous picolinate oxygen, O_2) are the most sensitive on the differences in the various complexes. The atomic charges of the nitrogens change within 0.03 e and show no clear trend in their variations.

The metal charges can be grouped into three groups according to the character of the metal, reflected also by their electronegativities. The p-block In and Bi (with

Table 1 QTAIM (Bader) charges of selected atoms in the $M(bispa^2)(H_2O)_x^+$ ($x = 0-2$) complexes (e)

M	EN ^a	$M(bispa^2)^+$		$M(bispa^2)(H_2O)^+$		$M(bispa^2)(H_2O)_2^+$	
		q_M	q_{O1}	q_M	q_{O1}	q_M	q_{O1}
Bi	1.67	1.84	−1.15	1.87	−1.18	1.90	−1.18
In	1.49	1.82	−1.18	-	-	-	-
Lu	1.14	2.14	−1.20	2.16	−1.22	2.20	−1.22
La	1.08	2.14	−1.20	2.16	−1.22	2.17	−1.22
Ac	1.00	2.28	−1.23	2.30	−1.24	2.30	−1.24

^aAllred-Rochow electronegativity of M in Pauling units [58, 59]

larger electronegativities, thus propensities for covalent bonding) have the smallest positive charges in the studied complexes, while Ac (with the smallest electronegativity, having a strong preference for ionic bonding) has the largest positive charge. The atomic charges being around +2 confirm the electrostatic interactions being the major contributions in the bonding, as expected from the strong anionic (-2 e) character of the bispa^2 ligand too. The anionic character is manifested in the Bader charges of the picolinate oxygens (around -1.2 e) at the first place, being in the closest contact with the metal cations. Accordingly, the O_1 (and the similar O_2) charges roughly follow the variations in the metal charges. The pyridine N charges are also around -1.2 e (showing only slight variations) while N_5 and N_6 in the bispidine scaffold have somewhat lower values (around -1.0 e).

The strongest charge transfer (CT) to the M^{III} ions occurs to the p-block metals (In, Bi), their low-energy valence p orbitals being excellent acceptor orbitals. The higher-energy 5d/6s (mixed with 4f in the case of La) orbitals of the lanthanides can gain less from CT, while the weakest CT interaction is managed by the even higher-energy valence orbitals of Ac.

The H_2O ligands transfer only marginal charge (up to 0.06 e) to the M^{III} ions in the $\text{M}(\text{bispa}^2)(\text{H}_2\text{O})_x^+$ ($x = 1-2$) complexes (cf. Table S4). Hence, the bispa^2 ligand is the main contributor to the covalent bonding (in form of donor–acceptor interactions) in the complexes. The coordination of H_2O increases slightly the magnitude of the M and O_1 charges (cf. Table 1). This can be explained by the above shown

increased M- bispa^2 distances, which result in less CT from bispa^2 to M.

Another computed parameter characterizing the covalent interactions in the complexes is the delocalization index. This integral property estimates the number of electrons forming the covalent bonding between M and the donor atoms of the ligands (and in this way the covalent bond order). Delocalization indices between M and the donor heteroatoms in the $\text{M}(\text{bispa}^2)^+$ complexes are depicted in Fig. 6 (the depicted values are compiled in Table S5 together with those of the hydrated derivatives).

It should be noted that Fig. 6 does not reflect the energetics of covalent interactions, because it depends on the energies of the acceptor orbitals too. The smaller metals have lower-energy acceptor orbitals, where the same number of shared electrons results in a stronger covalent bonding in terms of energy. In addition, Fig. 6 is only roughly related to the bispa^2 -to-M CT, because part of the transferred M valence electron densities are localized in the appropriate M orbitals and do not take part in electron sharing interactions.

The main message of the data in Fig. 6 is the contribution of the various donor heteroatoms to the covalent bonding between M and bispa^2 . Thus, the major donor is the picolinate oxygen (O_1, O_2), in the case of In comparable with the picolinate nitrogens (N_1, N_2). The latter donors have a considerable (towards Ac decreasing) contribution in the other complexes, too. The pyridine nitrogens (N_3, N_4) have comparable contributions to those of the bispidine scaffold except for the In complex, where the pyridine group containing N_4 is crowded out from the sterically strained vicinity of In

Fig. 6 Delocalization indices (e) between M and the donor heteroatoms in the $\text{M}(\text{bispa}^2)^+$ complexes. Contributions from the analogous donors are summed up. The presented values are given in Table S5 of the Supplementary Information

(vide supra). The main features in the curves of Fig. 6 are in fair correlation with the bond distances presented in Fig. 2. Due to the slightly increased bond distances in the hydrated $M(\text{bispa}^2)(\text{H}_2\text{O})_x^+$ ($x=1-2$) complexes, those delocalization indices are slightly smaller (cf. Table S5). The delocalization indices between M and the H_2O ligands are comparable to those of the bispidine nitrogens. In the $\text{M}-\text{O}(\text{H}_2)$ bonding, the covalent interaction seems to be a minor bonding contribution, because the H_2O oxygen has a high negative charge (cf. Table S3).

Energetics

The computed stabilities of the $M(\text{bispa}^2)(\text{H}_2\text{O})_x^+$ ($x=0-2$) complexes are demonstrated by the dissociation energetics in Fig. 7 in terms of electronic energies of the isolated molecules as well as Gibbs free energies in aqueous solution at 298 K. The corresponding data as well as energies of metal–metal exchange reactions are given in Tables S6 and S7, respectively, of the Supplementary Information.

The trend in Fig. 7a corresponds to a decreasing stability of the bispa^2 complexes with increasing M^{III} size in the case of the isolated molecule model. The gradual decrease deviates at the Bi complexes and may be attributed to the relatively stronger covalent bonding in them (cf. Fig. 6). The coordinating H_2O molecules (missing for In, vide supra) contribute to the stability of the complexes with all the metals. This can be seen in both the larger total dissociation energies and the endothermic dissociation of the H_2O

molecules with dissociation energies between 50 and 170 kJ/mol. The stability of H_2O -coordination increases with the M^{III} size parallel with that of the cavities in H_2O -free $M(\text{bispa}^2)^+$.

The situation changes drastically in the aqueous solution at 298 K (Fig. 7b). First, the dissociation energies are considerably smaller due to the strong stabilizing effect on the ionic dissociation products by the polar water solvent [60–62]. Second, the dissociation of the H_2O ligands becomes slightly exothermic upon thermal energy and solvation effects. This is in agreement with the observed H_2O -exchange in solution [28]. Also the stability of the $M(\text{bispa}^2)(\text{H}_2\text{O})_x^+$ complexes is considerably decreased, particularly those of In and Lu with the smallest ionic radii. These small M^{III} ions have very high solvation energies in water, and this larger stabilization of solvated In^{III} and Lu^{III} ions as dissociation products supports the dissociation of the parent complexes. The destabilized H_2O -coordination under these conditions decreases the total dissociation energies of the $M(\text{bispa}^2)(\text{H}_2\text{O})_x^+$ ($x=1,2$) complexes below those of the $M(\text{bispa}^2)^+$ ones, too.

It should be noted that the dissociation energies are likely underestimated by the LC pseudopotential of Ac. In a recent study of the $\text{Ac}(\text{macropa})$ complex [34], underestimation by 50 and 48 kJ/mol was found for the electronic (in vacuum) and Gibbs free energies (in solution) of dissociation by the LC pseudopotential (unpublished results). An underestimation in this magnitude would not change the trends in Fig. 7, whereas it would predict a stability of the solvated $\text{Ac}(\text{bispa}^2)$ complex significantly closer to those of La.

Fig. 7 Dissociation energies (kJ/mol) of the $M(\text{bispa}^2)(\text{H}_2\text{O})_x^+$ ($x=0-2$) complexes to the presented dissociation products in terms of **a** BSSE-corrected electronic energy of the isolated molecules at 0 K and **b** BSSE-

corrected Gibbs free energies in aqueous solution at 298 K. The presented values are given in Table S6 of the Supplementary Information

Altogether, supporting recent experimental observations [16, 28], the computations resulted in high stabilities of the bispa² complexes in aqueous solution for all the five studied metals. The computed stability order of In^{III} >> La^{III} > Lu^{III} for their bispa² complexes is in agreement with experimental stability constants determined by potentiometric titrations [16].

Conclusions

In the paper, a theoretical study of complexes of radionuclides relevant for nuclear medicine (In^{III}, Bi^{III}, Lu^{III}, Ac^{III} and additionally La^{III}) with the octadentate bispa derivative, H₂bispa², is reported. The study was performed by means of density functional theory calculations modelling both the isolated molecules and aqueous solution conditions.

The theoretical level was chosen on the basis of previous good experience with the TPSSh meta-hybrid functional [31–35] and test calculations on the In(bispa²)⁺ complex compared with the crystal structure of [In(bispa²)](TFA) [16]. As a result of the tests, relativistic pseudopotentials for the metals in conjunction with valence triple-zeta bases and the D3BJ dispersion correction were selected.

The deprotonated ligand formed octadentate M(bispa²)⁺ complexes with all the metals covered in the present study. The encapsulation proved to be complete for In^{III}, leaving not enough space for additional coordination of a H₂O ligand. The larger size of the other metals, however, facilitated the coordination of two H₂O molecules resulting in decadentate M(bispa²)(H₂O)₂⁺ complexes. The bonding of these H₂O ligands belongs to the weakest in these complexes, comparable to those of the bispidine nitrogens. From the eight heteroatoms of bispa², the anionic picolinate oxygens play the main role in both the (major) ionic and (minor) covalent metal-ligand interactions.

The stability of the isolated complex molecules at 0 K follows the size of the metal, decreasing from In to Ac. In aqueous solution under ambient conditions, the In and Bi complexes are the most stable, having comparable stability. Close stability was obtained for the Lu and La complexes, while the Ac complex remained the least stable. The high solvation energies of In^{III} and Lu^{III} may be particularly responsible for the break of the trend mentioned above for the isolated molecules: the stabilization of these dissociation products supports the dissociation of their parent complexes with respect to the others.

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Availability of data and material Benchmark calculations on In(bispa²)⁺, the values depicted in Figs. 1–7, metal–metal exchange energies, additional Bader atomic charges and Cartesian coordinates of the optimized structures are available as electronic supplementary material.

Declarations

Ethics approval The ethical standards have been met.

Conflict of interest The author declares no competing interests.

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