Metal–ligand interactions in complexes of cyclen-based ligands with Bi and Ac

Attila Kovács¹ · Zoltán Varga²

Received: 7 June 2021 / Accepted: 22 July 2021 / Published online: 18 August 2021
© The Author(s) 2021

Abstract

The structural and bonding properties of Bi and Ac complexes with cyclen-based chelating ligands have been studied using relativistic DFT calculations in conjunction with TZ2P all-electron basis sets. Besides the parent cyclen ligand, the study has covered its extensions with pyridine-type (L^{py}), carboxylate (DOTA, DOTPA), picolinate (MeDO2PA) and phosphonate (DOTMP) pendant arms. The effect of the cyclen ring size has been probed by increasing it from [12]aneN₄ to [16]aneN₄. Additional extensions in the DOTA complexes included the H₂O ligand at the 9th coordination site as well as the p-SCN-Bn substituent (a popular linker to the targeting vector). The study focuses on the complex stability, the nature of bonding and the differences between Ac and Bi in the complexes. The metal–ligand interactions have been analysed by the Extended Transition State method combined with Natural Orbitals of Chemical Valence theory and Quantum Theory of Atoms in Molecules models.

Keywords Bismuth · Actinium · Radiopharmaceuticals · Chelating ligands · Bonding

Introduction

Since 1936, the first treatment of a 28-year-old leukaemia patient with radioactive ³²P [1], the therapeutic applications of radioisotopes [2] emerged to a powerful tool in medicine. The method is particularly efficient in treating cancer and other cases of abnormal tissue growth [3], in which the ionizing radiation breaks the DNA molecules and so prevents their replication. In targeted radiotherapy, the radioisotopes can be transferred directly to the diseased cells. This is achieved by a biological targeting vector (antibody or peptide that has affinity for cancer cells) containing the chelated radionuclide [4]. The chelating molecule has a significant role in the method: the stability of the chelate complexes determines the efficiency of the radioisotope transfer as well

as the departure of the (generally also radioactive) decay products from the body.

One of the most prominent radiopharmaceuticals is the actinium ²²⁵Ac isotope. Utilizing its favourable α -emission (100%, $T_{1/2}$ = 240 h, E = 5600–5830 keV), it can be applied for the treatment of a range of cancers by means of targeted α therapy (TAT). It already has reached an advanced level of clinical tests [5–8] showing very good preliminary results in curing metastatic castration-resistant prostate cancer [9–11], acute myeloid leukaemia [12, 13] and neuroendocrine tumours [14].

The bismuth ²¹³Bi isotope ($T_{1/2}$ = 45.6 min) is a decay product of ²²⁵Ac and also a suitable TAT agent [15, 16]. Though the α -emission of ²¹³Bi is only 2.2% vs the 97.8% β -emission, the presence of pure α -emitting ²¹³Po and β -emitting ²⁰⁹Pb and ²⁰⁹Tl among its short-lived daughter radionuclides results in a high therapeutic efficacy. It has been successfully applied in a large number of preclinical studies and several clinical trials for treating glioma, glioblastoma [17, 18], neuroendocrine tumours [19] and prostate cancer [20]. Furthermore, ²¹³Bi is under investigation for treatment of leukaemia [21, 22] and melanoma [23, 24].

One of the superior chelators for both radiopharmaceuticals is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H₄DOTA) [17, 25, 26]. Disadvantages, however, are

Dedicated to the 80th birthday of Prof. István Hargittai!

✉ Attila Kovács
attila.kovacs@ec.europa.eu

¹ European Commission, Joint Research Centre (JRC), Karlsruhe, Germany

² Department of Chemistry, Chemical Theory Center, Minnesota Supercomputer Institute, University of Minnesota, Minneapolis, MN 55455, USA

its high affinity for other metal ions, preference for smaller ions [27] and slow radiolabelling kinetics. From this reason, extensive research is in progress on other suitable chelating ligands.

The chemical properties of the two cations important from the point of view of chelate formation are as follows: (i) both metals prefer the trivalent cation, M^{3+} , form [28–30]; (ii) Ac^{3+} has the largest 3+ effective ionic radius (1.12 Å, 6-coordinate) in the periodic system—that of 6-coordinate Bi^{3+} is 1.03 Å, essentially the same as that of La^{3+} [31, 32]; and (iii) Ac^{3+} is the most basic trivalent ion known [30]. As Ac has the smallest electronegativity (0.7) in the periodic system, the Ac^{3+} ion has a strong preference for ionic bonding. Due to its larger electronegativity of 1.62, the bonding of Bi^{3+} has a borderline-hard character with relatively high covalent contribution [28, 29].

In the present work, we study the structural and bonding properties of Bi and Ac complexes with cyclen-based chelating ligands using relativistic DFT calculations. The main goals are to uncover the effect of various functional groups on the cyclen heterocycle including the extension of its size from [12]- to [16]ane N_4 on the complex stability, the nature of bonding and the differences between Ac and Bi in the complexes. The metal–ligand interactions are analysed by the Extended Transition State method combined with Natural Orbitals of Chemical Valence theory (ETS-NOCV) [33] and Quantum Theory of Atoms in Molecules (QTAIM) [34–36] models.

Computational details

The calculations were performed with the Amsterdam Density Functional package (ADF2018 [37, 38]). The scalar relativistic effects were taken into account using the Zero-Order Regular Approximation (ZORA) [39]. The hybrid PBE0 exchange–correlation functional [40, 41] was used in conjunction with TZ2P all-electron basis sets consisting of uncontracted sets of Slater-type orbitals (STOs) optimized for use with ZORA [42]. The small frozen-core approximation was applied. This level of theory has been used in several recent studies on TAT-related complexes [43–46]. An auxiliary set of s, p, d, f and g STOs was used to fit the molecular density and to represent the Coulomb and exchange potentials accurately in each SCF cycle. Due to the closed-shell character of the complexes, they were treated using the spin-restricted formalism. The minimum characters of the analysed structures were confirmed by frequency calculations (instead of the expensive numerical Hessian in ADF by means of the Gaussian 09 code [47] using the SDD basis set [48–50], following the geometry optimization at this level).

The effect of spin–orbit (SO) interactions [51, 52] was probed on the $Bi(DOTA)^-$ and $Ac(DOTA)^-$ complexes. The SO effect proved to be negligible for the Bi while marginal for the Ac complex (it moves Ac^{3+} slightly closer to the cyclen nitrogens). The Extended Transition State (ETS) energy decomposition [53, 54] and Quantum Theory of Atoms in Molecules (QTAIM [34, 55, 56]) analyses were performed also with ADF2018 [37].

Our ETS energy decomposition analysis covered the following energy terms: the interaction energy between the M^{3+} and ligand fragments, ΔE_{int} , is defined as

$$\Delta E_{int} = \Delta V_{elst} + \Delta E_{Pauli} + \Delta E_{oi} \quad (1)$$

where ΔV_{elst} corresponds to the classical electrostatic interaction between the charge distributions of the isolated fragments after brought together in the complex, ΔE_{Pauli} is the repulsion between occupied orbitals (practically the steric repulsion) and ΔE_{oi} is the orbital interaction energy between the fragments in the complex, accounting for electron pair bonding, charge transfer and polarization [54]. In addition, ΔE_{oi} was further decomposed according to NOCV theory [33].

Ligands

The cyclen-based ligands form an important group of chelators for radiopharmaceuticals (Fig. 1). The cyclen (1,4,7,10-tetraazacyclododecane, **1**) parent can establish tetradentate interactions in 1:1 complexes due to its (only) four N donor atoms. Though **1** is not a relevant chelator for radiopharmaceuticals, this neutral ligand is involved in the present comparative analysis for reference purposes in order to measure the effects of the various functional groups in the pendant arms and the extension of macrocycle size.

Nitrogen-rich macrocyclic ligands possessing pyridine-type pendant arms proved recently to be efficient Bi-selective chelating agents [43] utilizing the soft Lewis acid character of Bi^{3+} . Four such neutral ligands are included in the present study, viz., 1,4,7,10-tetrakis(pyridin-2-ylmethyl)-1,4,7,10-tetraazacyclododecane (L^{py} , **2**), 1,4,7,10-tetrakis(3-pyridazylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pyd} , **3**), 1,4,7,10-tetrakis(4-pyrimidylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pyr} , **4**) and 1,4,7,10-tetrakis(2-pyrazinylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pz} , **5**). The pendant donors facilitate octadentate coordination to the metal ion, with somewhat different strength due to the difference in their relative basicity and chemical hardness. In addition, the large pendant arms can shield the metal and sterically hinder a coordination of additional small molecules (e.g., H_2O).

The MeDO2PA (6,6'-((4,10-dimethyl-1,4,7,10-tetraazacyclododecane-1,7-diyl)bis(methylene))

Fig. 1 List of ligands. The 2D structure of each ligand is given in Fig. S1 in the Supplementary Information

dipicolinic acid, **6**) molecule differs from the other ligands investigated in the present study in the coordination mode: it achieves an octacoordination with two pendant arms only utilizing both the pyridine N and carboxylate O donors of a picolinic acid arm. It has recently been investigated for Bi^{3+} , and larger complex stability with respect to DOTA has been found [57, 58]. The crystal structure of $Bi(\text{MeDO2PA})(\text{NO}_3)$ has been determined by X-ray diffraction [57].

DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, **7**) is one of the primary workhorse chelators for radiopharmaceuticals achieving the title of “gold standard” for a number of isotopes, including ^{111}In , ^{177}Lu , $^{86/90}\text{Y}$, ^{225}Ac and $^{44/47}\text{Sc}$. It is a traditional chelator for Bi^{3+} as well [2]. The ligand is applied in the form of 4- anion and by means of the N and carboxylate O donors forms octa-coordinated complexes with these metal ions. Accordingly, the molecular complex with Bi^{3+} and Ac^{3+} has a 1- charge. In the X-ray diffraction study of Bi-DOTA the counterion was Na^+ [59].

The small size of the pendant arms leaves some space on the top side of the complex. In aqueous solutions the coordination of a H_2O molecule to large coordinatively unsaturated metal ions (like La^{3+} , Ac^{3+}) has been observed [60, 61]. However, the H_2O ligand was shown to lack a significant influence on the stability of actinide and $La(\text{DOTA})^-$ complexes [45]. We investigated the effect of H_2O at the 9th coordination site in model **8**. Another noteworthy issue is the effect of the moiety linking the complex with the targeting vector. Preferably, the linker is on the ethylene diamine bridge in order to avoid direct interference with metal binding. We probed the p-SCN-Bn substituent with DOTA (2-[(4-isothiocyanatophenyl)methyl]-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, **9**) for its effect on the metal–ligand bonding. Structural data are available for $Ln\text{-DOTA-p-NO}_2\text{-Bn-DOTA}$ complexes (the NO_2 group being the precursor of SCN) from NMR studies [62]. The p- NO_2 -benzyl substituent was shown to effectively lock the conformation of the ring into the $\delta\delta\delta\delta$ configuration. The kinetic and thermodynamic stabilities were reported to

be slightly lower than those of the $Ln(\text{DOTA})$ complexes but still sufficiently high for in vivo application.

The effect of macrocycle enlargement is probed by the ligands TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid, **10**) and HETA (1,5,9,13-tetraazacyclohexadecane-1,5,9,13-tetraacetic acid, **11**). These ligands are based on a [14]ane N_4 and [16]ane N_4 macrocycle respectively, and besides the four N donors have four carboxylate O donors. TETA has good coordination properties to Cu [63], but with trivalent metals (e.g., La, Gd), lower stability was found than with DOTA [64]. Little is known about the HETA ligand. Nevertheless, on the basis of the large macrocycle, it is expected to favour large metals.

In the DOTPA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrapropionic acid, **12**) ligand larger flexibility is introduced with respect to DOTA, as the pendant arms are elongated by a methylene group. This ligand is rather unexplored: in the only study found in the literature it has been probed for ^{225}Ac but no radiolabelling was observed [65].

In order to probe other acidic, but non-carboxylate, oxygen donors, the DOTMP ligand (((1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(methylene))tetrakisphosphonic acid, **13**) with phosphonate pendant arms was included in the ligand set. This chelator has been considered as a bone-seeking agent with various radiopharmaceuticals (^{111}In , ^{166}Ho , ^{153}Sm , ^{177}Lu , ^{212}Bi) [66–71]. It has also been probed for ^{225}Ac and substantial radiolabelling was observed [65].

We note that some of the above ligands (DOTA, HETA, DOTPA, DOTMP) have recently been included in a study aiming computer-assisted chelator design for ^{225}Ac [46].

General structural characteristics

For geometry optimizations, the initial structures of the complexes were constructed from the following literature data: complexes with ligands **2–5** from the optimized geometries in [43]; with ligand **6** from the crystal structure of $Bi(\text{MeDO2PA})(\text{NO}_3)$ [57]; with ligands **7–8** from optimized geometries in [72]; with ligand **10** from the crystal structure

Fig. 2 Perspective view of metal–ligand interactions in the $M(\text{DOTA})^-$ complex: **a** top; **b** side. Hydrogen atoms are omitted for clarity

of Eu-TETA in [73]; and with ligands **11**, **12** and **13** from the computed geometries in [46]. We also probed additional isomers of **11** and **12** complexes which then proved to be lower in energy than those published in [46]. Complexes with ligand **1** were derived from the optimized geometry of $\text{Ac}(\text{DOTA})^-$ [72]. Those with ligand **9** were constructed on the basis of NMR results on the precursor Eu-DOTA-p- NO_2 -Bn [62], testing additionally the rotation of the p-SCN-Bn substituent. All complexes correspond to the TSAP isomer, known to be the favoured one of large metal ions with DOTA-like ligands [74].

The characteristic octadentate coordination of the DOTA ligand to metal ions is shown in Fig. 2 in two perspectives. The coordination of the other ligands covered in the present study are analogous with the exception of MeDO2PA, where the picolinic acid arm coordinates with two donor heteroatoms (pyridine N and carboxylate O) and the $\text{R}=\text{CH}_3$ substituent has no bonding interaction with M^{3+} .

The donor–acceptor bond distances are shown in Fig. 3. The values presented in the figure as well as the Cartesian coordinates of the optimized structures are given in the Supplementary Information.

Fig. 3 Metal–ligand bond distances ($\text{\AA}$) in the computed complexes. For ligand numbers, see Fig. 1. The symbol pairs in the case of C_2 and C_1 structures indicate the range of different values

Most of the optimizations converged to structures with C_4 or C_2 symmetry (compiled in the Supplementary Information). In general, the Bi complexes proved to be somewhat more symmetric than the Ac ones. In particular, the C_4 symmetries of the Bi complexes with the L^{py} -type ligands (2–5) were slightly deformed to C_2 symmetry in the Ac analogues. A similar slight C_4 -to- C_2 deformation was observed for the $Ac(DOTMP)^{5-}$ complex as well. The complexes with the HETA and the DOTA-p-SCN-Bn ligands are strongly asymmetric, the differences in the metal–ligand bond distances scattering up to 0.09 Å (cf. Table S1; Fig. 3).

Single crystal X-ray diffraction data are available for $Bi(MeDO2PA)(NO_3)$ [57] and $NaBiDOTA$ [59]; the measured M–N/O distances are included in Table S1. Comparison to the present computed data revealed that the ZORA-PBE0/TZ2P level overestimated considerably the M– N_{cyc} distances (similarly to computations at other DFT levels on related complexes [75]) and underestimated the M– X_{arm} distances. However, the deviations are not systematic which points to the importance of the different solid-state environments (counterions, intermolecular interactions, crystal packing) in the two crystalline materials.

The metal–ligand (M–N/O) bond distances in Fig. 3 reflect the following main features:

- (i) In agreement with the larger Ac^{3+} ionic radii, the bond distances in the Ac complexes are longer than in the Bi complexes. However, the differences between the Ac and Bi complexes (generally ca. 0.2 Å) exceed considerably the 0.09-Å difference in the metal ionic radii (6-coordinate radii are 1.12 vs 1.03 Å, no 8-coordinate radius is available for Ac^{3+}) [31]. The only exception is the M– N_{cyc} distance of the DOTMP complexes with a difference of 0.04 Å. The strong electrostatic interactions with the PO_3^{2-} groups of this highly negative ligand seem to pull the small Bi^{3+} effectively away from the cyclen moiety.
- (ii) Introduction of the carboxylate O donors in ligands 6–13 results in a significant increase in the M– N_{cyc} bond distances.
- (iii) The variation of the M–ligand distances agrees well for Bi^{3+} and Ac^{3+} with all the 13 ligands.

Bonding

The main results from the energy decomposition analysis are compiled in Table 1, while selected data are shown in Fig. 4.

The following assessment of bonding in the studied complexes is grouped according to the charges of the model structures. This procedure is reasoned by the significantly different intrinsic interaction energies (ΔE_{int}) with the variously charged ligands based on the largely different

electrostatic contributions (ΔV_{elst}). Accordingly, ΔE_{int} values with the neutral ligands (1–5) are very low, due to the small ΔV_{elst} contributions being lower than the covalent ΔE_{oi} . In contrast, in the complexes with the other charged ligands the ΔV_{elst} contributions dominate, being up to five times larger in the case of phosphonate donor groups. Accordingly, the latter DOTMP complexes have three times larger interaction energies than the ones with the neutral L^{py} -type ligands. The complexes with DOTA $^{4-}$ -type ligands have two-times larger interaction energies than those with L^{py} -type ligands. On the other hand, the markedly different ligand charges do not influence significantly the Pauli and orbital interaction contributions, as they vary only within a few hundred kilojoules per mole.

It should be noted that the significantly different ΔE_{int} data in the differently charged model structures have no direct relation to the experimentally found stabilities in solution, where the counterions, the solvation effects, the kinetics of complex formation and the stabilization of the free ligand can compensate effectively the differences in the isolated ion models. For example, the $Bi-L^{py}$ complex was reported to have a slightly larger stability in EDTA solution than $Bi-DOTA$ [43], while the Bi^{3+} - L^{py} intrinsic interaction energy is only half of that with DOTA $^{4-}$ (cf. Table 1).

Comparison to the tetradentate cyclen ligand shows that the octacoordination by the additional donors of the pendant arms significantly enhances the complex stabilities. The addition of the weak pyridine-type donors (2–5) increased the intrinsic interaction energy already by ca. 30% with respect to cyclen. This was achieved by the increase of both the electrostatic and orbital interactions as well as by the decrease of the Pauli interactions by a few hundred kilojoules per mole. The interaction energies are further increased by the anionic pendant arms of the other ligands.

The effects of minor changes in the ligands can be well seen in the L^{py} and DOTA series. From the L^{py} -type ligands, the most stable in terms of ΔE_{int} is the $M-L^{pyd}$ for both Bi and Ac complexes. Their ΔE_{int} values are slightly larger than those of $M-L^{py}$. In experimental EDTA-challenge studies of the $Bi-L^{py}$ -type complexes, similarly, these two ones were found to be superior [43], but with opposite stability order. As the data in Table 1 show, the lower stability of the $M-L^{pyr}$ and $M-L^{pz}$ complexes can mainly be attributed to the considerably weaker electrostatic interactions. The strongest (calculated) $M-L^{pyd}$ interaction is accompanied by significant differences in the geometry and atomic charges. In a unique way among the L^{py} -type ligands, in $M-L^{pyd}$ the $M-N_{arm}$ bonds are significantly shorter than the $M-N_{cyc}$ bonds, while with the other three L^{py} -type ligands the two metal–ligand bonds are comparable (cf. Fig. 3). The longer $M-N_{arm}$ distances in the latter three complexes reflect the steric effect of the CH hydrogen ortho-positioned to N_{arm} in the heterocycle. Also, the charge of N_{arm} in the $M-L^{pyd}$ complexes is very

Table 1 Main results from the ETS analysis of the Bi and Ac complexes^a

M	Ligand	ΔE_{int}	ΔE_{Pauli}	ΔV_{elst}	ΔE_{oi}	% _{elst/oi}
Bi	1 (Cyclen)	−2188.7	1014.5	−1395.8	−1807.4	44
	2 (L ^{py})	−2894.6	772.5	−1637.0	−2030.0	45
	3 (L ^{pyd})	−2937.6	784.5	−1693.9	−2028.2	46
	4 (L ^{pyr})	−2739.4	765.0	−1499.5	−2004.9	43
	5 (L ^{pz})	−2691.5	761.1	−1449.1	−2003.4	42
	6 (MeDO2PA)	−4663.8	1050.1	−3606.1	−2107.8	63
	7 (DOTA)	−6351.8	871.0	−5288.7	−1934.1	73
	8 (DOTA + H ₂ O) ^b	−5868.5	875.2	−5056.1	−1687.6	75
	9 (DOTA-p-SCN-Bn)	−6246.5	871.4	−4985.3	−2132.6	70
	10 (TETA)	−6398.2	948.2	−5336.3	−2010.1	73
	11 (HETA)	−6420.0	997.9	−5316.7	−2101.2	72
	12 (DOTPA)	−6388.4	860.7	−5261.5	−1987.6	73
	13 (DOTMP)	−9608.2	782.2	−8344.6	−2045.8	80
Ac	1 (Cyclen)	−1438.7	751.1	−1121.2	−1068.6	51
	2 (L ^{py})	−2278.5	817.7	−1533.8	−1562.4	50
	3 (L ^{pyd})	−2376.1	755.3	−1594.1	−1537.2	51
	4 (L ^{pyr})	−2126.2	803.9	−1395.3	−1534.8	48
	5 (L ^{pz})	−2073.7	795.5	−1342.8	−1526.4	47
	6 (MeDO2PA)	−4018.0	960.1	−3371.3	−1606.8	68
	7 (DOTA)	−5737.1	876.7	−5102.3	−1511.5	77
	8 (DOTA + H ₂ O) ^b	−5444.6	817.4	−4889.2	−1372.8	78
	9 (DOTA-p-SCN-Bn)	−5641.7	881.6	−4859.4	−1663.9	74
	10 (TETA)	−5733.3	884.1	−5087.1	−1530.3	77
	11 (HETA)	−5709.0	859.0	−5025.0	−1543.0	77
	12 (DOTPA)	−5764.1	855.2	−5061.6	−1557.7	76
	13 (DOTMP)	−8939.5	712.5	−8088.4	−1563.6	84

ΔE_{int} means the intrinsic interaction energy between the two fragments M^{3+} and ligand, %_{elst/oi} the ratio of the bonding electrostatic and covalent contributions evaluated as $\Delta V_{\text{els}}/(\Delta V_{\text{els}} + \Delta E_{\text{oi}}) \cdot 100$ (%)

^aEnergy data from energy decomposition analysis in kilojoules per mole

^bTwo-fragment model $M(H_2O)^{3+} + DOTA^{4-}$

small (ca. half of that in the other L^{py}-type complexes, cf. Table S2). The significant differences are the consequence of the neighbouring nitrogens in L^{pyd}. This N=N bond has a pronounced double-bond character (bond order of 1.48 in terms of the delocalization indices, vide infra) in contrast to the weaker aromatic N=C bonds (bond order 1.2) in the other ligands. The more covalent N=N moiety in L^{pyd} leads to less polarized charge distribution in the pyridazine ring (see footnote of Table S2).

The ETS results confirm the larger propensity of Bi³⁺ for the neutral L^{py}-type ligands as compared to Ac³⁺, in agreement with the expectations based on the borderline-hard character of Bi³⁺. This can be seen in the considerably larger ΔE_{oi} values than those of the Ac-L^{py}-type complexes, providing the major source for the larger ΔE_{int} of the Bi complexes.

The picolinic acid arms of the MeDO2PA ligand introduce a carboxylate oxygen in the metal–ligand interactions. Due to the fixed arrangement of the N and O atoms within a picolinic

acid moiety, the steric effects expressed by the ΔE_{Pauli} term are the largest with this ligand. The coordination of the pendant arms is determined by the carboxylate O. These complexes have the shortest M–O distances (implying very strong M–O interactions) while the M–N_{arm} distances are also considerably shorter than the M–N_{cyc} ones (cf. Fig. 3). The M–N_{cyc} interactions seem to be comparable with those in the complexes with DOTA-type ligands (7–10).

Metal-DOTA interactions have been analysed in several studies [43, 45, 46, 72, 74, 76–78]. The reported preference of the DOTA ligand for smaller metals can be clearly seen in the larger ΔE_{int} of Bi-DOTA (by 600 kJ/mol) vs Ac-DOTA. While both the electrostatic and covalent terms are larger in the Bi complex, the major contributor for its preference is the ΔE_{oi} term.

The H₂O ligand at the 9th coordination site decreases the energy of the M-DOTA interaction by 8 and 5% for M=Bi and Ac, respectively. The larger effect on Bi-DOTA is in agreement with the smaller ionic radius of Bi³⁺, hence its

Fig. 4 Energy decomposition results on the M–ligand interaction: **a)** ratio of electrostatic and covalent contributions to the bonding; **b)** interaction energy (kJ/mol)

less suitability for the 9th coordination. By inspecting the energy terms, no significant change upon H_2O coordination can be observed in the Pauli interaction. Decreases of similar magnitude occurred in the electrostatic and orbital interaction contributions of the two complexes related to the increasing distances between M and the donor heteroatoms of DOTA. The ratio of electrostatic and orbital contributions changed slightly for the favour of the electrostatic interaction.

The bonding energy of H_2O was evaluated by ETS analysis of the two-fragment model $\text{M}(\text{DOTA})^- + \text{H}_2\text{O}$. The resulted ΔE_{int} energies of around -40 kJ/mol confirmed the very weak bonding of H_2O at the 9th coordination site while the $\%_{\text{elst/ori}}$ ratios were similar (around 70%) as in the $\text{M}^{3+}\text{-DOTA}^{4-}$ interactions.

The p-SCN-Bn substituent on the DOTA ligand has only a small weakening effect (ca. 100 kJ/mol) on the metal–ligand interaction. The effects are larger on the specific bonding contributions, but the ca. 300 kJ/mol weaker electrostatic interactions are effectively compensated by the ca. 200 kJ/mol stronger covalent contributions.

The increase of the cyclen cavity with methylene groups in the TETA and HETA ligands resulted only in slight changes in the interaction energies. For Bi a gradual increase, while for Ac a gradual decrease in the order DOTA–TETA–HETA was obtained. The ratio of electrostatic and orbital contributions changed only marginally for the favour of orbital interactions. The M–donor distances suggest that the focus of bonding is slightly shifted towards

the pendant arms in the larger ligands: the M–O distances decreased with the ring size (strengthening of M–O interactions) while the M– N_{cyc} distances increased (weakening of M– N_{cyc} interactions), particularly in the HETA complexes. However, the two effects seem to compensate each other effectively leading to the conclusion: the cavity of the [12]–[16]ane N_4 rings with four N donors is not an important issue for the coordination of Bi^{3+} and Ac^{3+} . Recently, Morgenstern et al. also found more stable bonding of (the large) Ac^{3+} with 5N and 6N macrocycles as compared to 4N ones, hence increasing the number of coordinating heteroatoms parallel with the ring size [46].

The case is similar for the cavity of the carboxylate arms: extending the arms by a methylene group in the ligand DOTPA resulted in a slight increase of the M– N_{cyc} and a slight decrease of the M–O distances, achieving a slight increase of both the Bi and Ac complex stabilities.

Coordination by phosphonate O in ligand DOTMP seems to be sterically less demanding than with the carboxylate O in the DOTA-type complexes. In fact, the Pauli repulsion is the smallest in this Ac complex, while comparable to the smallest ones in the L^{py} -type complexes of Bi. The M–O distances imply M–O interactions comparable to those with the DOTA-type ligands. In contrast, on the basis of the longest M– N_{cyc} distances, these interactions may be the weakest here within the studied complexes.

Figure 4 provides an overview of the intrinsic interaction energies (ΔE_{int}) and the ratios of the electrostatic and orbital interactions ($\Delta V_{\text{elst}}/\Delta E_{\text{oi}}$) in the Bi and Ac complexes. The

metal–ligand interactions are consistently (though only in a small extent) stronger in the Bi complexes with all the probed ligands. In agreement with the expectations, the ionic bonding is somewhat more prominent in the Ac complexes as compared with their Bi analogues. The propensity of Ac for ionic interactions is manifested particularly in the negatively charged DOTA-derivative and DOTMP complexes.

The NOCV analysis provided further details on the covalent bonding in the complexes. The major contributions in the covalent charge transfer (CT) interactions of selected complexes are shown in Table 2 (additional NOCV data are given in Table S4). These data support an energetically more favourable CT to the 6p acceptor orbitals of Bi as compared to the 6d acceptor orbitals of Ac. The NOCV energies of the former main contributions are ca. twice larger. On the other hand, Ac has more opportunities for CT due to its five acceptor 6d orbitals (cf. Table 2; Fig. 5), while 7s appeared often as a minor contributor. The higher-energy orbitals of the metals (Bi 5d and 4f, Ac 5f) could be recognised occasionally as minor contributors in the lower-energy NOCVs.

The donor heteroatom orbitals appear in most cases mixed in the NOCVs. Pure O 2p or N 2p donations as well as separate interactions of the cyclen and pendant arm moieties could be observed only in a few cases. In the Ac complexes a larger contribution of O 2p vs N 2p orbitals was found as compared to the Bi complexes.

Selected data from the QTAIM analysis are shown in Fig. 6. They include the charge transferred from the ligands to M^{3+} (Δq) as derived from the Bader atomic charges, as well as the delocalization indices (DI) of the M–N and M–O bonds. The latter integral property indicates 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). The depicted values are given in Table S2 extended with the atomic charges of M and the donor heteroatoms of the ligand.

The above shown larger covalent bonding in the Bi complexes is manifested in ca. twice larger electron transfers as compared to the Ac complexes (cf. Fig. 6). Similarly, the larger positive Bader charge of Ac (around +2.3 e) is in agreement with the larger $\%_{\text{elst/oi}}$ data of these complexes (cf. Table 1). These characters are also in agreement with the electron density and its Laplacian data at the M–N and M–O bond critical points compiled in Table S3 of the Supplementary Information.

A characteristic feature is the variation of CT within 0.4 e (between +1.68 and +2.07 e) in the Bi complexes reflecting a significant difference between the CT properties of the L^{py} -type and DOTA-based ligands. The lower CT in the latter complexes is obviously due to the involvement of oxygen anions in the bonding, inclined more for ionic interactions. The variation is very small within the two groups. On the other hand, the CT in the Ac complexes is less ligand dependent (varies within 0.1 e) as another sign of the suppressed covalent interactions in these compounds.

Table 2 Major NOCV contributions in the charge transfer interactions of selected complexes^a

M	Ligand	ΔE	M orbital	Ligand orbital
Bi	2 (L^{py})	−316.2	Bi 6p _z	N 2p
		−310.9	Bi 6p _x	N 2p
		−310.9	Bi 6p _y	N 2p
	6 (MeDO2PA)	−345.3	Bi 6p _z	N _{cyc} 2p, O 2p
		−289.7	Bi 6p _y	N 2p
		−285.7	Bi 6p _x	N 2p, O 2p
	7 (DOTA)	−290.2	Bi 6p _z	N 2p
		−289.1	Bi 6p _y	O 2p, N 2p
		−289.1	Bi 6p _x	O 2p, N 2p
	13 (DOTMP)	−296.2	Bi 6p _x	O 2p
		−296.2	Bi 6p _y	O 2p
		−283.6	Bi 6p _z	N 2p
Ac	2 (L^{py})	−154.8	Ac 6d _{xy}	N 2p
		−148.4	Ac 6d _{xz}	N 2p
		−148.0	Ac 6d _{yz}	N 2p
		−98.2	Ac 6d _{x2-y2} , 5f _{xyz}	N 2p
		−86.8	Ac 7s	N 2p
		−79.3	Ac 6d _{z2} , 5f _{z3}	N 2p
	6 (MeDO2PA)	−179.2	Ac 6d _{xz} , 6d _{yz}	O 2p, N _{cyc} 2p
		−143.8	Ac 6d _{xy} , 6d _{x2-y2}	O 2p, N 2p
		−138.6	Ac 6d _{z2} , 6d _{x2-y2}	N _{arm} 2p, O 2p
		−123.0	Ac 6d _{yz} , 6d _{xz}	N _{cyc} 2p
		−88.2	Ac 6d _{x2-y2} , 6d _{xy} , 7s	O 2p, N _{arm} 2p
	7 (DOTA)	−163.9	Ac 6d _{xy}	O 2p
		−135.2	Ac 6d _{xz}	N 2p
		−135.2	Ac 6d _{yz}	N 2p
		−107.5	Ac 6d _{z2}	N 2p
		−93.7	Ac 6d _{x2-y2} , 6d _{xy}	O 2p
	13 (DOTMP)	−178.7	Ac 6d _{xy}	O 2p
		−139.6	Ac 6d _{yz}	N 2p
		−139.1	Ac 6d _{xz}	N 2p
		−133.3	Ac 6d _{z2}	N 2p
		−106.0	Ac 6d _{z2} , 7s	O 2p
		−101.6	Ac 6d _{x2-y2}	O 2p

^aEnergy contributions to the ΔE_{oi} term (ΔE , kJ/mol), main acceptor M and donor heteroatom orbitals of the ligand in the NOCV (N_{cyc} and N_{arm} mean the nitrogens in the cyclen and pendant arm moieties, respectively)

The covalent interactions of the two donor moieties of the ligands (the cyclen ring and the pendant arms) can be distinguished on the basis of the delocalization indices. According to the data depicted in Fig. 6, they are comparable in the case of the L^{py} -type ligands and are (only) slightly larger in these Bi complexes. In contrast, they differ significantly in the case of the DOTA-based ligands: here an increased number of bonding electrons from the anionic pendant arms can be observed (partly) for the cost of the cyclen nitrogens. Hence, in these complexes the charged pendant arms dominate not only the electrostatic, but also the covalent bonding.

Fig. 5 Characteristic NOCVs of the Ac(DOTA)[−] complex with the five Ac 6d acceptor orbitals. H atoms are omitted for clarity

Fig. 6 Characteristics of the covalent bonding in the complexes: transferred charge (Δq , e) and delocalization indices (e)

Conclusions

The radioactive isotopes of Bi and Ac are important radiopharmaceuticals and their complexation properties belong to the key points of their therapeutic application. In addition, the ²¹³Bi isotope is a decay product of ²²⁵Ac, and in this way playing an important role in the departure of radioactivity from the body after treatment with ²²⁵Ac. In order to support the development of efficient chelating agents for the two

radiopharmaceuticals, their bonding properties with selected popular ligands has been determined in the present study. We uncovered the structural and bonding effects of various popular pendant arms and other extensions of the cyclen ring for Bi and Ac complexes.

The selected ligands covered purely N donors (cyclen, L^{py}-type ligands) and anionic oxygen donors on the cyclen basis (Me-DO2PA, DOTA, TETA, HETA, DOTPA, DOTMP). The molecular geometries proved to

be symmetric (C_4 or C_2) in most cases. For some ligands, the C_4 symmetry of the Bi complex was decreased to C_2 in the Ac analogue (L^{PY} -type, DOTMP), implying a significant steric preference of the smaller Bi^{3+} ions compared to Ac^{3+} . The M-ligand distances vary parallel for Bi^{3+} and Ac^{3+} with all the 13 ligands studied.

The bonding energetics has been analysed using the ETS-NOCV energy decomposition model. The metal–ligand interactions are slightly stronger in the Bi complexes with all the probed ligands. This is based on the significantly stronger orbital interactions of Bi, while the ionic bonding is somewhat more prominent in the Ac complexes. The H_2O ligand binds very weakly at the 9th coordination site (the interaction energy is by two magnitudes of order smaller than the one of M-DOTA), yet it can decrease the M-DOTA interaction energy by notable extent (5–8%). Small changes in the cavity of the [12]ane N_4 ring and in the size of the carboxylate arms do not seem to be important issues for the coordination of Bi^{3+} and Ac^{3+} .

The NOCV analysis supported energetically more favourable charge transfer interactions with the 6p orbitals of Bi as compared to the 6d orbitals of Ac. The higher-energy orbitals of the metals (Bi 5d and 4f, Ac 5f) could be recognized occasionally as minor contributors in the lower-energy NOCVs. The charge transfer to Bi^{3+} is characteristically different in the cases of the neutral and charged ligands, while is less ligand-dependent in the Ac complexes. CT interactions from the two donor moieties of the L^{PY} -type ligands are comparable. In the complexes with DOTA-based ligands the charged pendant arms dominate not only the electrostatic, but the covalent bonding as well.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1007/s11224-021-01816-9>.

Author contribution Both authors contributed to the study conception and design. The calculations using the ADF code were performed by Z. Varga, the Gaussian 09 ones by A. Kovács. The data analysis and the first draft of the manuscript were made by A. Kovács, and both authors commented on subsequent versions of the manuscript. All the authors read and approved the final manuscript.

Funding The calculations have been carried out using resources provided by the affiliations of the authors (Minnesota Supercomputer Institute and JRC Karlsruhe site).

Data availability The geometries (Cartesian coordinates) optimized at the ZORA-PBE0/TZ2P level; data depicted in Figs. 3, 4 and 6; and additional QTAIM (electron densities, Laplacians of electron density, total energy densities at the bond critical points) and ETS-NOCV data are available as Electronic Supplementary Material.

Declarations

Ethics approval The ethical standards have been met.

Conflict of interest The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Williams JE (1999) Donner Laboratory: the birthplace of nuclear medicine. *J Nucl Med* 40:16N–20N
- Kostelnik TI, Orvig C (2019) Radioactive main group and rare earth metals for imaging and therapy. *Chem Rev* 119(2):902–956. <https://doi.org/10.1021/acs.chemrev.8b00294>
- Stewart AJ, Cormack RA, Held KD (2015) Radiobiologic concepts for brachytherapy. In: Devlin P, Cormack RA, Holloway CL, Stewart AJ (eds) *Brachytherapy. Applications and Techniques*. Springer Publishing Company, New York, pp 37–52. <https://doi.org/10.1891/9781617052613.0002>
- Milenic DE, Brechbiel MW (2004) Targeting of radio-isotopes for cancer therapy. *Cancer Biol Ther* 3(4):361–370. <https://doi.org/10.4161/cbt.3.4.790>
- Geerlings MW, Kaspersen FM, Apostolidis C, Van Der Hout R (1993) The feasibility of ^{225}Ac as a source of α -particles in radio-immunotherapy. *Nucl Med Commun* 14(2):121–125. <https://doi.org/10.1097/00006231-199302000-00009>
- Miederer M, Scheinberg DA, McDevitt MR (2008) Realizing the potential of the Actinium-225 radionuclide generator in targeted alpha particle therapy applications. *Adv Drug Delivery Rev* 60(12):1371–1382. <https://doi.org/10.1016/j.addr.2008.04.009>
- Thiele NA, Wilson JJ (2018) Actinium-225 for targeted α therapy: coordination chemistry and current chelation approaches. *Cancer Biother Radiopharm* 33(8):336–348. <https://doi.org/10.1089/cbr.2018.2494>
- Morgenstern A, Apostolidis C, Kratochwil C, Sathekge M, Krolicki L, Bruchertseifer F (2018) An overview of targeted alpha therapy with ^{225}Ac and ^{213}Bi . *Curr Radiopharm* 11(3):200–208. <https://doi.org/10.2174/1874471011666180502104524>
- Kratochwil C, Bruchertseifer F, Giesel FL, Weis M, Verburg FA, Mottaghy F, Kopka K, Apostolidis C, Haberkorn U, Morgenstern A (2016) ^{225}Ac -PSMA-617 for PSMA-targeted α -radiation therapy of metastatic castration-resistant prostate cancer. *J Nucl Med* 57(12):1941–1944. <https://doi.org/10.2967/jnumed.116.178673>
- Kratochwil C, Bruchertseifer F, Rathke H, Bronzel M, Apostolidis C, Weichert W, Haberkorn U, Giesel FL, Morgenstern A (2017) Targeted α -therapy of metastatic castration-resistant prostate cancer with ^{225}Ac -PSMA-617: dosimetry estimate and empiric dose finding. *J Nucl Med* 58(10):1624–1631. <https://doi.org/10.2967/jnumed.117.191395>
- Hammer S, Hagemann UB, Zitzmann-Kolbe S, Larsen A, Ellingsen C, Geraudie S, Grant D, Indrevoll B, Smeets R, von Ahsen O, Kristian A, Lejeune P, Hennekes H, Karlsson J, Bjerke RM, Ryan OB, Cuthbertson AS, Mumberg D (2020) Preclinical efficacy of a PSMA-targeted thorium-227 conjugate (PSMA-TTC), a targeted alpha therapy for prostate cancer. *Clin Cancer Res* 26(8):1985–1996. <https://doi.org/10.1158/1078-0432.CCR-19-2268>
- Jurcic JG, Rosenblat TL, McDevitt MR, Pandit-Taskar N, Carrasquillo JA, Chaneil SM, Zikaras K, Frattini MG, Maslak

- PM, Cicic D, Larson SM, Scheinberg DA (2013) Targeted alpha-particle nano-generator actinium-225 (^{225}Ac)-lintuzumab (anti-CD33) in acute myeloid leukemia (AML). *Clin Lymphoma, Myeloma Leuk* 13:S379–S380
13. Jurcic JG, Ravandi F, Pagel JM, Park JH, Douglas Smith B, Douer D, Yair Levy M, Estey E, Kantarjian HM, Earle D, Cicic D, Scheinberg DA (2015) Phase I trial of α -particle therapy with actinium-225 (^{225}Ac)-lintuzumab (anti-CD33) and low-dose cytarabine (LDAC) in older patients with untreated acute myeloid leukemia (AML). *J Clin Oncol* 33:7050–7050. https://doi.org/10.1200/jco.2015.33.15_suppl.7050
 14. Kratochwil C, Bruchertseifer F, Giesel F, Apostolidis C, Haberkorn U, Morgenstern A (2015) Ac-225-DOTATOC - an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors. *J Nucl Med* 56(Suppl. 3):1232
 15. Tafreshi NK, Doligalski ML, Tichacek CJ, Pandya DN, Budzevich MM, El-Haddad G, Khushalani NI, Moros EG, McLaughlin ML, Wadas TJ, Morse DL (2019) Development of targeted alpha particle therapy for solid tumors. *Molecules* 24(23):4314. <https://doi.org/10.3390/molecules24234314>
 16. Jadvar H (2020) Targeted α -therapy in cancer management: synopsis of preclinical and clinical studies. *Cancer Biother Radiopharm* 35(7):475–484. <https://doi.org/10.1089/cbr.2019.3340>
 17. Cordier D, Forrer F, Bruchertseifer F, Morgenstern A, Apostolidis C, Good S, Müller-Brand J, Mäcke H, Reubi JC, Merlo A (2010) Targeted alpha-radionuclide therapy of functionally critically located gliomas with ^{213}Bi -DOTA-[Thi⁸, Met(^{62}Cu)¹¹]-substance P: a pilot trial. *Eur J Nucl Med Mol Imaging* 37(7):1335–1344. <https://doi.org/10.1007/s00259-010-1385-5>
 18. Morgenstern A, Bruchertseifer F, Apostolidis C (2011) Targeted alpha therapy with ^{213}Bi . *Curr Radiopharm* 4(4):295–305. <https://doi.org/10.2174/1874471011104040295>
 19. Kratochwil C, Giesel FL, Bruchertseifer F, Mier W, Apostolidis C, Boll R, Murphy K, Haberkorn U, Morgenstern A (2014) ^{213}Bi -DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. *Eur J Nucl Med Mol Imaging* 41(11):2106–2119. <https://doi.org/10.1007/s00259-014-2857-9>
 20. Kratochwil C, Afshar-Oromieh A, Kopka K, Haberkorn U, Giesel FL (2016) Current status of prostate-specific membrane antigen targeting in nuclear medicine: clinical translation of chelator containing prostate-specific membrane antigen ligands into diagnostics and therapy for prostate cancer. *Semin Nucl Med* 46(5):405–418. <https://doi.org/10.1053/j.semnuclmed.2016.04.004>
 21. Jurcic JG, Larson SM, Sgouros G, McDevitt MR, Finn RD, Divgi CR, Ballangrud AM, Hamacher KA, Ma D, Humm JL, Brechbiel MW, Molinet R, Scheinberg DA (2002) Targeted α particle immunotherapy for myeloid leukemia. *Blood* 100(4):1233–1239. https://doi.org/10.1182/blood.V100.4.1233.h81602001233_1233_1239
 22. Rosenblatt TL, McDevitt MR, Mulford DA, Pandit-Taskar N, Divgi CR, Panageas KS, Heaney ML, Chanel S, Morgenstern A, Sgouros G, Larson SM, Scheinberg DA, Jurcic JG (2010) Sequential cytarabine and α -particle immunotherapy with bismuth-213-lintuzumab (HuM195) for acute myeloid leukemia. *Clin Cancer Res* 16(21):5303. <https://doi.org/10.1158/1078-0432.ccr-10-0382>
 23. Raja C, Graham P, Rizvi S, Song E, Goldsmith H, Thompson J, Bosserhoff A, Morgenstern A, Apostolidis C, Kearsley J, Reisfeld R, Allen BJ (2007) Interim analysis of toxicity and response in phase I trial of systemic targeted alpha therapy for metastatic melanoma. *Cancer Biol Ther* 6(6):846–852. <https://doi.org/10.4161/cbt.6.6.4089>
 24. Allen BJ, Singla AA, Rizvi SMA, Graham P, Bruchertseifer F, Apostolidis C, Morgenstern A (2011) Analysis of patient survival in a Phase I trial of systemic targeted α -therapy for metastatic melanoma. *Immunotherapy* 3(9):1041–1050. <https://doi.org/10.2217/imt.11.97>
 25. Wild D, Frischknecht M, Zhang H, Morgenstern A, Bruchertseifer F, Boisclair J, Provencher-Bolliger A, Reubi JC, Maecke HR (2011) Alpha- versus beta-particle radiopeptide therapy in a human prostate cancer model (^{213}Bi -DOTA-PESIN and ^{213}Bi -AMBA versus ^{177}Lu -DOTA-PESIN). *Cancer Res* 71(3):1009–1018. <https://doi.org/10.1158/0008-5472.CAN-10-1186>
 26. Chan HS, Konijnenberg MW, de Blois E, Koelewijn S, Baum RP, Morgenstern A, Bruchertseifer F, Breeman WA, de Jong M (2016) Influence of tumour size on the efficacy of targeted alpha therapy with (213)Bi-[DOTA(0), Tyr(3)]-octreotate. *EJNMMI Res* 6(1):6. <https://doi.org/10.1186/s13550-016-0162-2>
 27. Cacheris WP, Nickle SK, Sherry AD (1987) Thermodynamic study of lanthanide complexes of 1,4,7-triazacyclononane-N, N', N''-triacetic acid and 1,4,7,10-tetraazacyclododecane-N, N', N'' N'''-tetraacetic acid. *Inorg Chem* 26(6):958–960. <https://doi.org/10.1021/ic00253a038>
 28. Norman NC (1998) Chemistry of arsenic, antimony and bismuth. Springer, Netherlands, Amsterdam
 29. Sadler PJ, Li H, Sun H (1999) Coordination chemistry of metals in medicine: target sites for bismuth. *Coord Chem Rev* 185–186:689–709. [https://doi.org/10.1016/S0010-8545\(99\)00018-1](https://doi.org/10.1016/S0010-8545(99)00018-1)
 30. Kirby HW, Morss LR (2006) Actinium. In: Morss LR, Edelstein NM, Fuger J (eds) The chemistry of the actinide and transactinide elements. Springer, Dordrecht, pp 18–51. https://doi.org/10.1007/1-4020-3598-5_2
 31. Shannon RD (1976) Revised effective ionic radii and systematic studies of interatomic distances in halides and chalcogenides. *Acta Cryst A* 32:751–767
 32. Huheey JE, Keiter EA, Keiter RL (1993) Inorganic chemistry : principles of structure and reactivity, 4th edn. HarperCollins, New York, USA
 33. Mitoraj MP, Michalak A, Ziegler T (2009) A combined charge and energy decomposition scheme for bond analysis. *J Chem Theor Comput* 5(4):962–975. <https://doi.org/10.1021/ct800503d>
 34. Bader RFW (1990) Atoms in Molecules. A Quantum Theory. Oxford University Press, Oxford
 35. Popelier PLA (2000) Atoms in molecules: an introduction. Prentice Hall, Harlow
 36. Matta CF, Boyd RJ (2007) An introduction to the quantum theory of atoms in molecules. In: Matta CF, Boyd RJ (eds) The quantum theory of atoms in molecules. Wiley-VCH, Weinheim, pp 1–34. <https://doi.org/10.1002/9783527610709.ch1>
 37. Amsterdam Density Functional Package (2020) SCM theoretical chemistry. Vrije Universiteit, Amsterdam, The Netherlands
 38. te Velde G, Bickelhaupt FM, Baerends EJ, Fonseca Guerra C, van Gisbergen SJA, Snijders JG, Ziegler T (2001) Chemistry with ADF. *J Comput Chem* 22(9):931–967. <https://doi.org/10.1002/jcc.1056>
 39. van Lenthe E, Baerends EJ, Snijders JG (1994) Relativistic total energy using regular approximations. *J Chem Phys* 101(11):9783–9792. <https://doi.org/10.1063/1.467943>
 40. Perdew JP, Burke K, Ernzerhof M (1996) Generalized gradient approximation made simple. *Phys Rev Letters* 77:3865–3868
 41. Adamo C, Barone V (1999) Toward reliable density functional methods without adjustable parameters: The PBE0 model. *J Chem Phys* 110:6158–6169. <https://doi.org/10.1063/1.478522>
 42. van Lenthe E, Baerends EJ (2003) Optimized Slater-type basis sets for the elements 1–118. *J Comput Chem* 24:1142–1156. <https://doi.org/10.1002/jcc.10255>
 43. Wilson JJ, Ferrier M, Radchenko V, Maassen JR, Engle JW, Batista ER, Martin RL, Nortier FM, Fassbender ME, John KD, Birnbaum ER (2015) Evaluation of nitrogen-rich macrocyclic ligands for the chelation of therapeutic bismuth radioisotopes. *Nucl Med Biol* 42(5):428–438. <https://doi.org/10.1016/j.nucmedbio.2014.12.007>

44. Kelley MP, Deblonde GJP, Su J, Booth CH, Abergel RJ, Batista ER, Yang P (2018) Bond covalency and oxidation state of actinide ions complexed with therapeutic chelating agent 3,4,3-LI(1,2-HOPO). *Inorg Chem* 57(9):5352–5363. <https://doi.org/10.1021/acs.inorgchem.8b00345>
45. Stein BW, Morgenstern A, Batista ER, Birnbaum ER, Bone SE, Cary SK, Ferrier MG, John KD, Pacheco JL, Kozimor SA, Mocko V, Scott BL, Yang P (2019) Advancing chelation chemistry for actinium and other +3 f-elements, Am, Cm, and La. *J Am Chem Soc* 141(49):19404–19414. <https://doi.org/10.1021/jacs.9b10354>
46. Morgenstern A, Lilley LM, Stein BW, Kozimor SA, Batista ER, Yang P (2021) Computer-assisted design of macrocyclic chelators for actinium-225 radiotherapeutics. *Inorg Chem* 60(2):623–632. <https://doi.org/10.1021/acs.inorgchem.0c02432>
47. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery Jr. JA, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Keith T, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas O, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ (2010) Gaussian 09, Revision D.01. Gaussian, Inc., Wallingford CT
48. Dunning TH Jr, Hay PJ (1977) Gaussian basis sets for molecular calculations. In: Schaefer HF (ed) *Modern theoretical chemistry* vol 3. Plenum, New York, pp 1–28
49. Küchle W, Dolg M, Stoll H, Preuss H (1991) Ab initio pseudopotentials for Hg through Rn. *Mol Phys* 74(6):1245–1263. <https://doi.org/10.1080/00268979100102941>
50. Moritz A, Cao X, Dolg M (2007) Quasirelativistic energy-consistent 5f-in-core pseudopotentials for trivalent actinide elements. *Theor Chem Acc* 117:473–481. <https://doi.org/10.1007/s00214-006-0180-7>
51. van Lenthe E, Snijders J, Baerends E (1996) The zero-order regular approximation for relativistic effects: the effect of spin-orbit coupling in closed shell molecules. *J Chem Phys* 105:6505–6516. <https://doi.org/10.1063/1.472460>
52. van Lenthe E, van Leeuwen R, Baerends EJ, Snijders JG (1996) Relativistic regular two-component Hamiltonians. *Int J Quantum Chem* 57:281–293. [https://doi.org/10.1002/\(SICI\)1097-461X\(1996\)57:3<3c281::AID-QUA2%3e3.0.CO;2-U](https://doi.org/10.1002/(SICI)1097-461X(1996)57:3<3c281::AID-QUA2%3e3.0.CO;2-U)
53. Ziegler T, Rauk A (1977) On the calculation of bonding energies by the Hartree Fock Slater method. The transition state method. *Theor Chim Acta* 46:1. <https://doi.org/10.1007/BF02401406>
54. Bickelhaupt FM, Baerends EJ (2000) Kohn-Sham density functional theory: predicting and understanding chemistry. In: Lipkowitz KB, Boyd DB (eds). *Rev Comput Chem* vol 15. Wiley-VCH, New York, pp 1–86
55. Rodríguez JJ, Köster AM, Ayers PW, Santos-Valle A, Vela A, Merino G (2009) An efficient grid-based scheme to compute QTAIM atomic properties without explicit calculation of zero-flux surfaces. *J Comput Chem* 30:1082–1092. <https://doi.org/10.1002/jcc.21134>
56. Rodríguez JJ, Bader RFW, Ayers PW, Michel C, Götz AW, Bo C (2009) A high performance grid-based algorithm for computing QTAIM properties. *Chem Phys Letters* 472:149–152. <https://doi.org/10.1016/j.cplett.2009.02.081>
57. Lima LMP, Beyler M, Oukhatar F, Le Saec P, Faivre-Chauvet A, Platas-Iglesias C, Delgado R, Tripier R (2014) H₂Me-d₂pa: an attractive chelator with fast, stable and inert ^{nat}Bi³⁺ and ²¹³Bi³⁺ complexation for potential α -radioimmunotherapy applications. *Chem Commun* 50(82):12371–12374. <https://doi.org/10.1039/c4cc05529b>
58. Lima LMP, Beyler M, Delgado R, Platas-Iglesias C, Tripier R (2015) Investigating the complexation of the Pb²⁺/Bi³⁺ pair with dipicolinate cyclen ligands. *Inorg Chem* 54(14):7045–7057. <https://doi.org/10.1021/acs.inorgchem.5b01079>
59. Csajbók É, Baranyai Z, Bányai I, Brucher E, Király R, Muller-Fahrnow A, Platzek J, Raduchel B, Schäfer M (2003) Equilibrium, ¹H and ¹³C NMR spectroscopy, and X-ray diffraction studies on the complexes Bi(DOTA)[−] and Bi(DO₃A-Bu). *Inorg Chem* 42(7):2342–2349. <https://doi.org/10.1021/ic0261272>
60. Aime S, Barge A, Botta M, Fasano M, J. DA, Bombieri G, (1996) Crystal structure and solution dynamics of the lutetium(III) chelate of DOTA. *Inorg Chim Acta* 246(1):423–429. [https://doi.org/10.1016/0020-1693\(96\)05130-4](https://doi.org/10.1016/0020-1693(96)05130-4)
61. Benetollo F, Bombieri G, Calabi L, Aime S, Botta M (2003) Structural variations across the lanthanide series of macrocyclic DOTA complexes: insights into the design of contrast agents for magnetic resonance imaging. *Inorg Chem* 42(1):148–157. <https://doi.org/10.1021/ic025790n>
62. Woods M, Kovacs Z, Kiraly R, Brücher E, Zhang S, Sherry AD (2004) Solution dynamics and stability of lanthanide(III) (S)-2-(p-nitrobenzyl)DOTA complexes. *Inorg Chem* 43(9):2845–2851. <https://doi.org/10.1021/ic0353007>
63. Clarke ET, Martell AE (1991) Stabilities of the alkaline earth and divalent transition metal complexes of the tetraazamacrocyclic tetraacetic acid ligands. *Inorg Chim Acta* 190(1):27–36. [https://doi.org/10.1016/S0020-1693\(00\)80228-5](https://doi.org/10.1016/S0020-1693(00)80228-5)
64. Clarke ET, Martell AE (1991) Stabilities of trivalent metal ion complexes of the tetraacetate derivatives of 12-, 13- and 14-membered tetraazamacrocycles. *Inorg Chim Acta* 190 (1):37–46. [https://doi.org/10.1016/S0020-1693\(00\)80229-7](https://doi.org/10.1016/S0020-1693(00)80229-7)
65. McDevitt MR, Ma D, Simon J, Frank RK, Scheinberg DA (2002) Design and synthesis of ²²⁵Ac radioimmunopharmaceuticals. *Appl Radiat Isot* 57(6):841–847. [https://doi.org/10.1016/s0969-8043\(02\)00167-7](https://doi.org/10.1016/s0969-8043(02)00167-7)
66. Hassfjell SP, Bruland ØS, Hoff P (1997) ²¹²Bi-DOTMP: an alpha particle emitting bone-seeking agent for targeted radiotherapy. *Nucl Med Biol* 24(3):231–237. [https://doi.org/10.1016/S0969-8051\(97\)00059-0](https://doi.org/10.1016/S0969-8051(97)00059-0)
67. Rajendran JG, Eary JF, Bensinger W, Durack LD, Vernon C, Fritzberg A (2002) High-dose ¹⁶⁶Ho-DOTMP in myeloablative treatment of multiple myeloma: pharmacokinetics, biodistribution, and absorbed dose estimation. *J Nucl Med* 43(10):1383–1390
68. Chakraborty S, Das T, Banerjee S, Chaudhari PR, Sarma HD, Venkatesh M, Pillai MRA (2004) Preparation and biological evaluation of ¹⁵³Sm-DOTMP as a potential agent for bone pain palliation. *Nucl Med Commun* 25(12):1169–1176. <https://doi.org/10.1097/00006231-200412000-00003>
69. Das T, Chakraborty S, Sarma HD, Banerjee S (2008) ¹⁷⁷Lu-DOTMP: a viable agent for palliative radiotherapy of painful bone metastasis. *Radiochim Acta* 96(1):55–61. <https://doi.org/10.1524/ract.2008.1464>
70. Simón J, Frank RK, Crump DK, Erwin WD, Ueno NT, Wendt RE (2012) A preclinical investigation of the saturation and dosimetry of ¹⁵³Sm-DOTMP as a bone-seeking radiopharmaceutical. *Nucl Med Biol* 39(6):770–776. <https://doi.org/10.1016/j.nucmedbio.2011.12.015>
71. Yousefnia H, Jalilian AR, Zolghadri S, Mirzaei A, Bahrami-Samani A, Mirzaei M, Ghannadi M (2015) Development of ¹¹¹In DOTMP for dosimetry of bone pain palliation agents. *J Radioanal Nucl Chem* 304(2):911–916. <https://doi.org/10.1007/s10967-014-3911-6>

72. Kovács A (2021) Theoretical study of actinide(III)-DOTA complexes. *ACS Omega* 6(20):13321–13330. <https://doi.org/10.1021/acsomega.1c01292>
73. Kang J-G, Na M-K, Yoon S-K, Sohn Y, Kim Y-D, Suh I-H (2000) Determination of the structure of EuTETA and the luminescence properties of EuTETA and EuDOTA (TETA=1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetate and DOTA=1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate). *Inorg Chim Acta* 310(1):56–64. [https://doi.org/10.1016/S0020-1693\(00\)00268-1](https://doi.org/10.1016/S0020-1693(00)00268-1)
74. Viola-Villegas N, Doyle RP (2009) The coordination chemistry of 1,4,7,10-tetraazacyclododecane-N, N', N'', N'''-tetraacetic acid (H4DOTA): structural overview and analyses on structure-stability relationships. *Coord Chem Rev* 253(13):1906–1925. <https://doi.org/10.1016/j.ccr.2009.03.013>
75. Roca-Sabio A, Regueiro-Figueroa M, Esteban-Gómez D, de Blas A, Rodríguez-Blas T, Platas-Iglesias C (2012) Density functional dependence of molecular geometries in lanthanide(III) complexes relevant to bioanalytical and biomedical applications. *Comput Theor Chem* 999:93–104. <https://doi.org/10.1016/j.comptc.2012.08.020>
76. Stasiuk GJ, Long NJ (2013) The ubiquitous DOTA and its derivatives: the impact of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid on biomedical imaging. *Chem Commun* 49(27):2732–2746. <https://doi.org/10.1039/c3cc38507h>
77. Frimpong E, Skelton AA, Honarparvar B (2017) DFT study of the interaction between DOTA chelator and competitive alkali metal ions. *J Mol Graph Modelling* 76:70–76. <https://doi.org/10.1016/j.jmgm.2017.06.025>
78. Pujales-Paradela R, Rodríguez-Rodríguez A, Gayoso-Padula A, Brandariz I, Valencia L, Esteban-Gómez D, Platas-Iglesias C (2018) On the consequences of the stereochemical activity of the Bi(III) 6s² lone pair in cyclen-based complexes. The [Bi(DO3A)] case. *Dalton Trans* 47 (39):13830–13842. <https://doi.org/10.1039/c8dt02602e>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.