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

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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 (Lpy), 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%, T1/2 = 240 h, Eα = 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 (T1/2 = 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 211Po 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...
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 groups on the cyclen heterocycle; including the extension of main goals are to uncover the effect of various functional chelating ligands using relativistic DFT calculations. The ing properties of Bi and Ac complexes with cyclen-based covalent contribution [28, 29].

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, \(\Delta E_{\text{int}}\), is defined as

\[
\Delta E_{\text{int}} = \Delta V_{\text{elst}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{oi}}
\]

where \(\Delta V_{\text{elst}}\) corresponds to the classical electrostatic interaction between the charge distributions of the isolated fragments after brought together in the complex, \(\Delta E_{\text{Pauli}}\) is the repulsion between occupied orbitals (practically the steric repulsion) and \(\Delta E_{\text{oi}}\) is the orbital interaction energy between the fragments in the complex, accounting for electron pair bonding, charge transfer and polarization [54]. In addition, \(\Delta E_{\text{oi}}\) 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-tetraazacyclododecanec, 1) parent can establish tetratentate interactions in 1:1 complexes due to its (only) four N door 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-tetraazacyclododecanec (L\(^{\text{py}}\), 2), 1,4,7,10-tetrakis(3-pyridazylmethyl)-1,4,7,10-tetraazacyclododecanec (L\(^{\text{pz}}\), 3), 1,4,7,10-tetrakis(4-pyrimidylmethyl)-1,4,7,10-tetraazacyclododecanec (L\(^{\text{pyd}}\), 4) and 1,4,7,10-tetrakis(2-pyrazinylmethyl)-1,4,7,10-tetraazacyclododecanec (L\(^{\text{pzpy}}\), 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\(_2\)O).

The MeDIO2PA \((6,6\'\'-(4,10-dimethyl-1,4,7,10-tetraazacyclododec-1,7-diyl)bis(methylene))"
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 \(\text{Bi}^{3+}\), and larger complex stability with respect to DOTA has been found [57, 58]. The crystal structure of \(\text{Bi(MeDO2PA)}(\text{NO}_3)\) 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 \(^{111}\text{In}, ^{177}\text{Lu}, ^{225}\text{Ac}\), and \(^{44}\text{Sc}\). It is a traditional chelator for \(\text{Bi}^{3+}\) as well [2]. The ligand is applied in the form of 4-anion and by means of the N and carboxylate O donors forms octacoordinated complexes with these metal ions. Accordingly, the molecular complex with \(\text{Bi}^{3+}\) and \(\text{Ac}^{3+}\) has a 1\(^-\) charge. In the X-ray diffraction study of Bi-DOTA the counterion was \(\text{Na}^+\) [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 \(\text{H}_2\text{O}\) molecule to large coordinatively unsaturated metal ions (like \(\text{La}^{3+}\), \(\text{Ac}^{3+}\)) has been observed [60, 61]. However, the \(\text{H}_2\text{O}\) ligand was shown to lack a significant influence on the stability of actinide and \(\text{La(DOTA)}^-\) complexes [45]. We investigated the effect of \(\text{H}_2\text{O}\) 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-DOTA-p-NO\(_2\)-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 \(\delta\delta\delta\delta\delta\delta\) configuration. The kinetic and thermodynamic stabilities were reported to be slightly lower than those of the \(\text{Ln(DOTA)}\) 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]aneN\(_4\) and [16]aneN\(_4\) 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 \(^{225}\text{Ac}\) 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))tetraphosphonic 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 (\(^{111}\text{In}, ^{166}\text{Ho}, ^{153}\text{Sm}, ^{177}\text{Lu}, ^{212}\text{Bi}\)) [66–71]. It has also been probed for \(^{225}\text{Ac}\) 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 \(^{225}\text{Ac}\) [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 \(\text{Bi(MeDO2PA)}(\text{NO}_3)\) [57]; with ligands 7–8 from optimized geometries in [72]; with ligand 10 from the crystal structure.
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 Ac(DOTA)$^-\text{[72]}$. 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 R = 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.
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 \( L^{P7} \)-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\(_\text{cyc} \) distances (similarly to computations at other DFT levels on related complexes \([75]\)) and underestimated the M-X\(_\text{arm} \) 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\(_\text{cyc} \) distance of the DOTMP complexes with a difference of 0.04 Å. The strong electrostatic interactions with the PO\(_4^{2–} \) 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\(_\text{cyc} \) 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 (\( \Delta E_{\text{int}} \)) with the variously charged ligands based on the largely different electrostatic contributions (\( \Delta V_{\text{elst}} \)). Accordingly, \( \Delta E_{\text{int}} \) values with the neutral ligands (1–5) are very low, due to the small \( \Delta V_{\text{elst}} \) contributions being lower than the covalent \( \Delta E_{\text{oi}} \). In contrast, in the complexes with the other charged ligands the \( \Delta V_{\text{elst}} \) 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 \( L^{P7} \)-type ligands. The complexes with DOTA\(^{4–} \)-type ligands have two-times larger interaction energies than those with \( L^{P7} \)-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 \( \Delta E_{\text{int}} \) 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\(^{P7} \) complex was reported to have a slightly larger stability in EDTA solution than Bi-DOTA \([43]\), while the Bi\(^{3+}-L^{P7} \) intrinsic interaction energy is only half of that with DOTA\(^{4–} \) (cf. Table 1).

Comparison to the tetradeptate 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 \( L^{P7} \) and DOTA series. From the \( L^{P7} \)-type ligands, the most stable in terms of \( \Delta E_{\text{int}} \) is the M-L\(_{P7}^{yd} \) for both Bi and Ac complexes. Their \( \Delta E_{\text{int}} \) values are slightly larger than those of M-L\(_{P7}^{7} \). In experimental EDTA-challenge studies of the Bi-L\(_{P7}^{yd} \)-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\(_{P7}^{yd} \) and M-L\(_{P7}^{7} \) complexes can mainly be attributed to the considerably weaker electrostatic interactions. The strongest (calculated) M-L\(_{P7}^{yd} \) interaction is accompanied by significant differences in the geometry and atomic charges. In a unique way among the L\(_{P7}^{yd} \)-type ligands, in M-L\(_{P7}^{yd} \) the M-N\(_\text{arm} \) bonds are significantly shorter than the M-N\(_\text{cyc} \) bonds, while with the other three L\(_{P7}^{yd} \)-type ligands the two metal–ligand bonds are comparable (cf. Fig. 3). The longer M-N\(_\text{arm} \) distances in the latter three complexes reflect the steric effect of the CH hydrogen ortho-positioned to N\(_\text{arm} \) in the heterocycle. Also, the charge of N\(_\text{arm} \) in the M-L\(_{P7}^{yd} \) complexes is very
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 Bi$^{3+}$ for the neutral $L_{py}$-type ligands as compared to Ac$^{3+}$, in agreement with the expectations based on the borderline-hard character of Bi$^{3+}$. This can be seen in the considerably larger $\Delta E_{\text{int}}$ values than those of the Ac-$L_{py}$-type complexes, providing the major source for the larger $\Delta E_{\text{int}}$ 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 $\Delta E_{\text{Pauli}}$ 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–Narm distances are also considerably shorter than the M–Ncyc ones (cf. Fig. 3). The M–Ncyc 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 $\Delta E_{\text{int}}$ 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 $\Delta E_{\text{oi}}$ term.

The $H_2O$ 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 Bi$^{3+}$, hence its

$\Delta E_{\text{int}}$ means the intrinsic interaction energy between the two fragments $M^{3+}$ and ligand, $\%_{\text{elst/oi}}$ the ratio of the bonding electrostatic and covalent contributions evaluated as $\Delta V_{\text{elst}}/(\Delta V_{\text{elst}} + \Delta E_{\text{oi}})\times100$ (%) .

Energy data from energy decomposition analysis in kilojoules per mole

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

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

| M  | Ligand            | $\Delta E_{\text{int}}$ | $\Delta E_{\text{Pauli}}$ | $\Delta V_{\text{elst}}$ | $\Delta E_{\text{oi}}$ | $\%_{\text{elst/oi}}$ |
|----|-------------------|-------------------------|-----------------------------|--------------------------|-------------------------|------------------------|
| 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 (DTPA)         | -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 (DTPA)         | -5764.1                 | 855.2                       | -5061.6                  | -1557.7                 | 76                     |
|    | 13 (DOTMP)        | -8939.5                 | 712.5                       | -8088.4                  | -1563.6                 | 84                     |

The $H_2O$ 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 Bi$^{3+}$, hence its...
less suitability for the 9th coordination. By inspecting the energy terms, no significant change upon H₂O 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 H₂O was evaluated by ETS analysis of the two-fragment model M(DOTA)⁻⁺H₂O. The resulted ΔE_{int} energies of around −40 kJ/mol confirmed the very weak bonding of H₂O at the 9th coordination site while the %elst/oi ratios were similar (around 70%) as in the M³⁺-DOTA⁴⁻ 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]aneN₄ rings with four N donors is not an important issue for the coordination of Bi³⁺ and Ac³⁺. Recently, Morgenstern et al. also found more stable bonding of (the large) Ac³⁺ 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 L³⁻subtype 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 (ΔV_{elst}/ΔE_{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 different acceptor orbitals (cf. Table 2, Fig. 5), while 7s appeared only as a minor contributor. The higher-energy orbitals of the Bi complexes (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 \(\%_{\text{elat}}\) 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\(^{P9}\)-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 (kJ/mol) | M orbital | Ligand orbital |
|-----|--------|-------------|-----------|---------------|
| Bi  | 2 (L\(^{P9}\)) | −316.2 | Bi 6p\(_1\) | N 2p |
|     |        | −310.9 | Bi 6p\(_1\) | N 2p |
|     |        | −310.9 | Bi 6p\(_1\) | N 2p |
| 6 (MeDO2PA) | −345.3 | Bi 6p\(_1\) | N\(_{\text{cyc}}\) 2p, O 2p |
| 7 (DOTA) | −289.2 | Bi 6p\(_1\) | N 2p |
|     | −285.7 | Bi 6p\(_1\) | N 2p, O 2p |
| 13 (DOTMP) | −289.1 | Bi 6p\(_1\) | O 2p, N 2p |
| Ac  | 2 (L\(^{P9}\)) | −154.8 | Ac 6d\(_{x^2}\) | N 2p |
|     |        | −184.8 | Ac 6d\(_{z^2}\) | N 2p |
|     |        | −184.0 | Ac 6d\(_{x^2}\) | N 2p |
|     |        | −98.2 | Ac 6d\(_{x^2}+6f_{xz}\) | N 2p |
|     |        | −86.8 | Ac 7s | N 2p |
|     |        | −79.3 | Ac 6d\(_{x^2}+5f_{z^2}\) | N 2p |
| 6 (MeDO2PA) | −179.2 | Ac 6d\(_{x^2}+6d_{z^2}\) | O 2p, N\(_{\text{cyc}}\) 2p |
|     | −143.8 | Ac 6d\(_{x^2}+6d_{z^2}+6f_{xz}\) | O 2p, N 2p |
|     | −138.6 | Ac 6d\(_{x^2}+6d_{z^2}+6f_{xz}\) | N\(_{\text{arm}}\) 2p, O 2p |
|     | −123.0 | Ac 6d\(_{x^2}+6d_{z^2}+6f_{xz}\) | N\(_{\text{cyc}}\) 2p |
|     | −88.2 | Ac 6d\(_{x^2}+6d_{z^2}+6f_{xz}\) | O 2p, N\(_{\text{arm}}\) 2p |
| 7 (DOTA) | −163.9 | Ac 6d\(_{x^2}\) | O 2p |
|     | −135.2 | Ac 6d\(_{z^2}\) | N 2p |
|     | −135.2 | Ac 6d\(_{z^2}\) | N 2p |
|     | −107.5 | Ac 6d\(_{z^2}\) | N 2p |
|     | −93.7 | Ac 6d\(_{x^2}+6d_{z^2}\) | O 2p |
| 13 (DOTMP) | −178.7 | Ac 6d\(_{x^2}\) | O 2p |
|     | −139.6 | Ac 6d\(_{z^2}\) | N 2p |
|     | −139.1 | Ac 6d\(_{z^2}\) | N 2p |
|     | −133.3 | Ac 6d\(_{z^2}\) | N 2p |
|     | −106.0 | Ac 6d\(_{x^2}+7s\) | O 2p |
|     | −101.6 | Ac 6d\(_{z^2}+7s\) | O 2p |

\(^a\)Energy contributions to the ΔE\(_{oi}\) term (ΔE, kJ/mol), main acceptor M and donor heteroatom orbitals of the ligand in the NOCV (N\(_{\text{cyc}}\) and N\(_{\text{arm}}\) mean the nitrogens in the cyclen and pendant arm moieties, respectively)
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 $^{213}$Bi isotope is a decay product of $^{225}$Ac, and in this way playing an important role in the departure of radioactivity from the body after treatment with $^{225}$Ac. 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 (C₄ or C₂) in most cases. For some ligands, the C₃ symmetry of the Bi complex was decreased to C₂ in the Ac analogue (L₉²-type, DOTMP), implying a significant steric preference of the smaller Bi³⁺ ions compared to Ac³⁺. The M-ligand distances vary parallel for Bi³⁺ and Ac³⁺ 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 H₂O 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]aneN₄ ring and in the size of the carboxylate arms do not seem to be important issues for the coordination of Bi³⁺ and Ac³⁺.

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 Bi³⁺ 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 L₉²-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.

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**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.

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**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.

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