Evaluation of Nitrogen-Rich Macrocyclic Ligands for the Chelation of Therapeutic Bismuth Radioisotopes

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Abstract

Introduction: The use of α -emitting isotopes for radionuclide therapy is a promising treatment strategy for small micro-metastatic disease. The radioisotope ^{213}Bi is a nuclide that has found substantial use for targeted α -therapy (TAT). The relatively unexplored aqueous chemistry of Bi^{3+} , however, hinders the development of bifunctional chelating agents that can successfully deliver these Bi radioisotopes to the tumor cells. Here, a novel series of nitrogen-rich macrocyclic ligands is explored for their potential use as Bi-selective chelating agents.

Methods: The ligands, 1,4,7,10-tetrakis(pyridin-2-ylmethyl)-1,4,7,10-tetraazacyclododecane (L^{py}), 1,4,7,10-tetrakis(3-pyridazylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pyd}), 1,4,7,10-tetrakis(4-pyrimidylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pyr}), and 1,4,7,10-tetrakis(2-pyrazinylmethyl)-1,4,7,10-tetraazacyclododecane (L^{pz}), were prepared by a previously reported method and investigated here for their abilities to bind Bi radioisotopes. The commercially available and commonly used ligands 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and *N*-[(*R*)-2-amino-3-(*p*-isothiocyanato-phenyl)propyl]-*trans*-(*S,S*)-cyclohexane-1,2-diamine-*N,N,N',N'',N''*-pentaacetic acid (CHX-A''-DTPA) were also explored for comparative purposes. Radio-thin-layer chromatography (TLC) was used to measure the binding kinetics and stabilities of the complexes formed. The long-lived isotope, ^{207}Bi ($t_{1/2} = 32$ years), was used for these studies. Density functional theory (DFT) calculations were also employed to probe the ligand interactions with Bi^{3+} and the generator parent ion Ac^{3+} .

Results: In contrast to DOTA and CHX-A''-DTPA, these nitrogen-rich macrocycles selectively chelate Bi^{3+} in the presence of the parent isotope Ac^{3+} . Among the four tested, L^{py} was found to exhibit optimal Bi^{3+} -binding kinetics and complex stability. L^{py} complexes Bi^{3+} more rapidly than DOTA, yet the resulting complexes are of similar stability. DFT calculations corroborate the experimentally observed selectivity of these ligands for Bi^{3+} over Ac^{3+} .

Conclusion: Taken together, these data implicate L^{py} as a valuable chelating agent for the delivery of ^{213}Bi . Its selectivity for Bi^{3+} and rapid and stable labeling properties warrants further investigation and biological studies.

Keywords: targeted α -therapy, bismuth-213, actinium-225, radiolabeling, radio-thin-layer chromatography, macrocycles

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1. Introduction

High-energy α -particles emitted by the decay of radioactive isotopes can be harnessed with an appropriate biological targeting vector to destroy malignant cells [1-3]. This therapeutic strategy, known as α -therapy, is the subject of intense current research, with its utility emphasized by the recent FDA-approval of the α -emitter $^{223}\text{RaCl}_2$ for the treatment of bone metastases arising from castration-resistant prostate cancer [4]. The short range (several cell diameters) and high linear energy transfer ($\approx 100 \text{ keV}/\mu\text{m}$) of emitted α -particles suggests their use in the treatment of micro-metastatic disease, where irradiation can be limited to the targeted cells. However, the limited availability of α -emitting nuclides with appropriate physical properties for therapy hinders their development for clinical application [5, 6].

Among the radionuclides proposed for targeted α -therapy (TAT), the decay chain of ^{213}Bi ($t_{1/2} = 45.6 \text{ m}$, 97.8% β^- , 2.2% α), which entails an α emission from either of two possible branches thanks to its α -emitting daughter, ^{213}Po ($t_{1/2} = 3.72 \mu\text{s}$, 100% α) has shown significant promise. The short half-life of ^{213}Bi is suitable for use with small-molecule and peptide-based targeting agents. Furthermore, its short half-life and small decay chain (Fig. 1) minimize toxic side effects that may arise from long-lived daughter nuclides, which can redistribute to non-target sites in vivo [7]. ^{213}Bi can also be conveniently obtained from a generator system comprised of its longer-lived parent ^{225}Ac ($t_{1/2} = 9.9 \text{ d}$, 100% α), which is attractive for clinical use [8-11]. Such generator systems are currently commercially available from Oak Ridge National Laboratory in the United States and the Institute for Transuranium Elements in Germany, with future commercial development underway at the Institute for Physics and Power Engineering in Russia [12]. Although the widespread availability of the ^{225}Ac parent isotope is limited currently, impeding the further development of ^{213}Bi pharmaceuticals [13], significant

progress has been made toward the large-scale production of ^{225}Ac [14-17]. The great therapeutic utility of ^{213}Bi is reflected by the several clinical trials that have employed this isotope for cancer treatment [18-23]. The potential of ^{213}Bi and other α -emitters for the treatment of infectious diseases is currently under intense investigation as well [24-26].

Fig. 1. Decay chain of ^{213}Bi , including ancestral isotopes from the ^{233}U decay series.

Despite the promise of ^{213}Bi TAT, the element bismuth has complicated aqueous chemistry, rendering its complexation for biological delivery challenging. The high affinity of Bi^{3+} for OH^- ($\log K = 12.9$) [27] indicates the strong tendency of this ion to hydrolyze at even at slightly acidic pH values. Challenges associated with the aqueous chemistry of Bi^{3+} have largely hindered the development and rational design of chelating ligands. Ligands currently used for TAT with ^{213}Bi are DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and CHX-A''-DTPA (*N*-[(*R*)-2-amino-3-(*p*-isothiocyanato-phenyl)propyl]-*trans*-(*S,S*)-cyclohexane-1,2-diamine-*N,N,N',N'',N'''*-pentaacetic acid), shown in Fig. 2. Radiolabeling kinetics for DOTA are generally slow, and both CHX-A''-DTPA and DOTA have high affinity for metal ions other than Bi^{3+} . The development of other bifunctional chelating agents for Bi^{3+} , which exhibit fast radiolabeling kinetics, high stability, and good metal ion selectivity, would be welcome additions to DOTA and CHX-A''-DTPA for ^{213}Bi TAT. A ligand that is highly selective for Bi^{3+} may minimize the effects of ^{225}Ac breakthrough from the $^{225}\text{Ac}/^{213}\text{Bi}$ generator, which may occur after operator error.

Recently, we described a series of nitrogen-rich macrocyclic ligands and explored their coordination chemistry with La^{3+} [28]. These ligands (Fig. 2), L^{py} (1,4,7,10-tetrakis(pyridin-2-ylmethyl)-1,4,7,10-tetraazacyclododecane), L^{pyd} (1,4,7,10-tetrakis(3-pyridazylmethyl)-1,4,7,10-tetraazacyclododecane), L^{pyr} (1,4,7,10-tetrakis(4-pyrimidylmethyl)-1,4,7,10-tetraazacyclododecane), and L^{pz} (1,4,7,10-tetrakis(2-pyrazinylmethyl)-1,4,7,10-tetraazacyclododecane), are structurally homologous, varying only in the nature of the pendant *N*-heterocyclic donors. The pendant donors vary in their relative basicity and chemical hardness values. In our previous work, we demonstrated how these subtle electronic modifications across this series of ligands have significant effects on the solution behavior of their La^{3+} complexes [28]. Here, we describe the utility of this class of ligands for the selective and stable chelation of radiobismuth. The fast radiolabeling kinetics, high stability, and good selectivity for Bi^{3+} over the generator parent Ac^{3+} indicate that these ligands may be useful for ^{213}Bi TAT.

Fig 2. Structures and abbreviated names of ligands investigated in this work.

2. Materials and methods

2.1. General

Aqueous buffers were prepared using 18 M Ω ·cm Milli-Q water obtained from a Millipore filtration system. Trace metal-free Optima-grade acids and bases used for adjusting pH were obtained from Fisher Scientific. Other buffer components were obtained from commercial vendors and were of the highest purity available. The ligands DOTA and CHX-A''-DTPA were

purchased from Fluka Scientific and Macrocyclics, Inc (Dallas, TX, USA), respectively. The other ligands, L^{py} , L^{pyd} , L^{pyr} , and L^{pz} , were synthesized as previously described [28, 29]. Alumina-backed silica gel thin-layer chromatography (TLC) plates were obtained from EMD Millipore. A Cyclone Plus Phosphor Imager from Perkin Elmer was used to visualize radioactivity on developed TLC plates. An Ortec (Oak Ridge, TN) p-type Al-windowed high purity Ge (HPGe) gamma spectrometer with a relative efficiency of approximately 15% was used to measure activities in the TLC plates ($FWHM_{1333\text{ keV}} = 1.9\text{ keV}$). The detector energy and efficiency calibration and background are checked regularly, and analysis of acquired spectra was accomplished with the Ortec GammaVision software package. For stable element analysis, inductively coupled plasma atomic emission spectroscopy (ICP-AES), using a Shimadzu ICPE-9000 instrument equipped with a $2\text{ cm} \times 2\text{ cm}$ CCD. Calibration solutions from Pb and Bi were prepared from certified stocks. All other elements were determined using a qualitative measurement method based on calibrating the response of the instrument to known concentrations of two reference elements, namely Al and Ba. Analyses were performed in triplicate and based on a 30 s sample exposure time. Output data were managed and analyzed using the ICPE solutions software version 1.01 (Shimadzu Corp. 2005).

^{225}Ac was obtained from ^{229}Th , which was taken from a historic LANL stock supply, immobilized on a column of anion exchange resin as the nitrate salt. The purity of ^{229}Th was verified by ICP-OES, revealing the absence of quasi-stable ^{232}Th , and gamma spectroscopy, signifying the absence of gamma-emitting isotopes other than those from the ^{229}Th decay chain. ^{225}Ac , a daughter of ^{229}Th , was eluted from the column and purified from ^{225}Ra , as previously described [9, 30], and obtained as the nitrate salt in 0.05 M HNO_3 . ^{207}Bi , as the nitrate salt in dilute nitric acid, was used from LANL Isotope Program stock supply. The purity of this sample

was verified by HPGe gamma spectroscopy and by ICP-AES, which revealed the absence of contaminating radioisotopes or substantial quantities of stable elements ($< 50 \mu\text{g/L}$ Bi and Pb). The presence of small quantities of ^{208}Bi ($t_{1/2} = 3.7 \times 10^7$ years, 100% EC), co-produced with ^{207}Bi from $^{\text{nat}}\text{Pb}(\text{p},\text{xn})$ reactions and beneath the detection limits of our spectroscopic equipment configurations, cannot be ruled out.

2.2. ^{225}Ac and $^{207/213}\text{Bi}$ selectivity studies

^{225}Ac (9 kBq, 0.02 pmol), 24 h after elution and purification from the ^{229}Th generator, was mixed with ^{207}Bi (3 kBq, 7.3 pmol) and ligand (1 mM, 500 nmol) in 0.1 M NH_4OAc at pH 5 and room temperature ($22 \pm 2^\circ\text{C}$) in a total reaction volume of 500 μL . At different time points, 5 μL aliquots were spotted on silica gel TLC plates. The plates were developed with a mobile phase of 0.4 M NaCitrate at pH 4 with 10% methanol. Under these conditions, free metal ions migrated with the solvent front ($R_f = 1$) and metal ions bound to the ligand remained at the baseline ($R_f = 0$). These R_f values were verified by phosphor imaging of the TLC plates (Fig. 3). After development, the TLC plates were cut in half ($R_f = 0.5$), and each half was measured by HPGe gamma spectroscopy. Reported uncertainties are derived from the statistical counting errors of the HPGe detector. The 218 keV gamma line of the ^{221}Fr daughter of ^{225}Ac was used to quantify the activity of Ac, whereas the 570 keV gamma line of ^{207}Bi was used for Bi quantification. The 440 keV gamma line of ^{213}Bi could also potentially be used. However, its short half-life (45.6 min) and continuing generation from the decay of ^{225}Ac limited its utility. Therefore, the use of ^{207}Bi as a longer-lived analogue ($t_{1/2} = 31.6$ years, 100% EC) enabled quantification of Bi^{3+} chelation properties of the ligands.

Fig. 3. Representative silica gel TLC plate, visualized with a phosphor imager. The mobile phase was 0.4 M NaCitrate pH 4.0 with 10% methanol.

2.3 ²⁰⁷Bi radiolabeling kinetics

In a total reaction volume of 500 μ L in a plastic Eppendorf tube, 3 kBq (7.3 pmol) of ²⁰⁷Bi was incubated with 10, 100, or 1000 μ M of the ligands tested. The rate of complexation was monitored by TLC. Aliquots (5 μ L) were spotted on silica gel TLC plates at different time points. The system used was the same as that described above. The activity was quantified by the 570 keV gamma emission of ²⁰⁷Bi. Variations in temperature were achieved by submerging the Eppendorf tubes in hot water baths. The pH was adjusted to desired values with glacial acetic acid or ammonium hydroxide.

2.4. EDTA-challenge stability studies

Bismuth-ligand complexes were formed by incubating 4.8 kBq (11.7 pmol) ²⁰⁷Bi and the ligand (0.5 mM, 60 nmol) in 120 μ L of 0.1 M phosphate-buffered saline (PBS) at pH 7.4 and room temperature (22 ± 2 °C). Radio-TLC of the reaction mixture after 24 h revealed >95% labeling of ²⁰⁷Bi. A 100 μ L portion of the labeled ²⁰⁷Bi solutions was diluted to a total volume of 500 μ L with EDTA dissolved in pH 7.4 0.1 M PBS. The final ligand concentration was 100 μ M and the final EDTA concentration was 50 mM. At different time points, 5 μ L aliquots of the reaction mixture were spotted on a silica gel TLC plate. For these studies a mobile phase of 0.1 M EDTA at pH 7.4 was used. EDTA-complexed metal ions migrated with the solvent front ($R_f = 1$), whereas the other complexes remained at the baseline ($R_f = 0$). As described above, the loss of ²⁰⁷Bi from the ligands was determined by cutting the TLC plates in half and measuring the activity on each end with a HPGe gamma spectrometer.

2.5. Cold metal ion stability studies

^{207}Bi -labeled complexes were prepared by the incubation of ligands (0.5 mM, 100 nmol) in 0.1 M 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer at pH 7.4 with 3 kBq (7.3 pmol) ^{207}Bi for 24 h at ambient room temperature (22 ± 2 °C) in a total volume of 200 μL . Quantitative (> 95%) radiolabeling of the ^{207}Bi was verified by radio-TLC. After 24 hours, the solution was split into 4 aliquots and the complexes were challenged with 0.1 μmol of cold metal in 100 mM MOPS (i.e., 0.5 mM metal and 0.11 mM ligand), bringing the solution to a total volume of 200 μL . At different time points, 5 μL aliquots of the reaction mixture were spotted on a silica gel TLC plate. For these studies, a mobile phase of 0.4 M NaCitrate at pH 4 with 10% methanol was used, as described above. The loss of ^{207}Bi from the ligands was determined by cutting the TLC plates in half and measuring the activity on each side with a HPGe gamma spectrometer.

2.6. DFT calculations

Density functional theory (DFT) calculations were carried out using *Gaussian09* [31]. The hybrid B3LYP functional was utilized [32, 33]. Ac, La, and Bi atoms were assigned the quasi-relativistic Stuttgart/Dresden (SDD) effective core potential [34]. The associated segmented basis set [35] was modified for Ac and La by removing g functions and removing the most diffuse functions, those with exponential constants of less than 0.05. Other atoms were given the Pople-style 6-31G(d) basis set [36, 37]. Geometry optimizations were carried out in the gas-phase. Starting geometries for optimizations were taken and modified as necessary from crystallographic data for $[\text{Bi}(\text{L}^{\text{py}})]^{3+}$ [38], $[\text{La}(\text{L}^{\text{py}})(\text{OH}_2)]^{3+}$ [28], $[\text{Bi}(\text{DOTA})]^{1-}$ [39], $[\text{La}(\text{DOTA})(\text{OH}_2)]^{1-}$ [40], and $[\text{Bi}(\text{CHX-DTPA})]^{2-}$ [41], where CHX-DTPA is the analogous ligand to CHX-A''-DTPA without the benzyl isothiocyanate group. The hydrated ion starting geometries were obtained from previous computational studies on a similar system [42].

Frequency calculations were employed to obtain thermodynamic parameters and to verify that all structures are local minima on the potential energy surface. Free energy values in water were calculated by single-point calculations of the gas-phase optimized structures in the SMD continuum solvation model [43]. Thermochemical corrections were taken from the gas-phase frequency calculations, adjusted for a pressure of 1354 atm due to the density of liquid water [44], and applied to the SCF energies of the single-point SMD-solution calculations to estimate free energy values in aqueous solution. Ligand strain energies were obtained from single-point energy calculations of the metal complexes in the absence of the metal ion. The SMD solvation model was applied for these calculations as well. Coordinates and energies of optimized structures are given in the Supplementary data.

3. Results

3.1. ^{225}Ac and ^{207}Bi competition study

The ability of the nitrogen-rich macrocycles, DOTA, and CHX-A''-DTPA to complex ^{225}Ac and Bi was investigated. ^{225}Ac was eluted from a ^{229}Th generator and purified from ^{225}Ra , as previously described [9, 30]. After reaching secular equilibrium with its daughters, a 9 kBq portion of ^{225}Ac was spiked with 4 kBq of ^{207}Bi . ^{207}Bi ($t_{1/2} = 32$ a) was used as a longer-lived surrogate for the short-lived therapeutically relevant ^{225}Ac daughter, ^{213}Bi ($t_{1/2} = 45.6$ min). The resulting radioisotope mixture was incubated with 1 mM ligand at pH 5 and room temperature. The labeling was monitored by radio-TLC, using the conditions described above in Section 2.2. The energy of the gamma emissions on the TLC plate could be used to identify specific isotopes. The 218 keV peak of short-lived ^{221}Fr , the immediate daughter of ^{225}Ac , provided a convenient handle to quantify the activity of actinium. Although ^{213}Bi has a convenient gamma line at 440 keV, its short half-life (45.6 min) and the presence of ^{225}Ac , which constantly generates more of

this isotope through decay, hinders its direct use for these studies. Hence, ^{207}Bi was introduced as a surrogate. The 32 year half-life and 570 keV gamma line of this isotope facilitate its use.

The quantity of ^{225}Ac - and ^{213}Bi -labeled ligands at different time points is given in Table 1. As Table 1 shows, the nitrogen-rich macrocycles fail to label ^{225}Ac even after 24 h. In contrast, quantitative labeling of ^{207}Bi is observed for all these ligands after 1 h. DOTA and CHX-A''-DTPA fail to show selectivity for Bi over Ac; after 24 h, all ^{225}Ac is bound by DOTA and 30% of the ^{225}Ac is complexed by CHX- A''-DTPA. These studies reveal that the nitrogen-rich macrocycles possess a distinct selectivity for Bi^{3+} over Ac^{3+} in contrast to the conventionally used polyamino carboxylate ligands.

Table 1. Results of ^{225}Ac and ^{207}Bi Competition Studies^a

	Time	L^{py}	L^{pyd}	L^{pyr}	L^{pz}	DOTA	CHX-A''-DTPA
% ^{225}Ac	30 min	0	0	0	0	44 $\pm$ 4	0
Bound	60 min	0	0	0	0	63 $\pm$ 5	9 $\pm$ 2
	24 h	0	0	0	0	94 $\pm$ 6	30 $\pm$ 3
% ^{207}Bi Bound	30 min	98 $\pm$ 7	97 $\pm$ 6	88 $\pm$ 6	77 $\pm$ 3	82 $\pm$ 6	98 $\pm$ 6
	60 min	100 $\pm$ 7	100 $\pm$ 7	96 $\pm$ 6	94 $\pm$ 6	86 $\pm$ 6	100 $\pm$ 8
	24 h	100 $\pm$ 6	100 $\pm$ 7	100 $\pm$ 7	100 $\pm$ 7	93 $\pm$ 6	100 $\pm$ 7

^a Conditions are described in Section 2.2. Reported uncertainties are derived from statistical counting errors of the HPGe detector.

3.2. ^{207}Bi radiolabeling kinetics

^{207}Bi (3 kBq, 7.3 pmol) was incubated with 100 μM (50 nmol) ligand in 1 M NH_4OAc at pH 5 and ambient temperature ($22 \pm ^\circ\text{C}$) to a total reaction volume of 500 μL . Kinetics were

probed using the same TLC system as described above in conjunction with HPGe gamma spectroscopy. Fig. 4 shows the kinetic trace for the radiolabeling reactions. Under these conditions, CHX-A''-DTPA complexes 90% of the ^{207}Bi after only 5 min. L^{py} is the second fastest ligand tested with >90% labeling observed after 30 min. Notably, it is faster than DOTA. The radiolabeling kinetics of the remaining three ligands follows the order $\text{L}^{\text{pyd}} > \text{L}^{\text{pyr}} > \text{L}^{\text{pz}}$.

Fig. 4. Radiolabeling kinetics of ^{207}Bi . The reaction was carried out in 1 M NH_4OAc at pH 5 and 22 ± 2 °C. A total reaction volume of 500 μL with 3 kBq of ^{207}Bi and 100 μM of ligand was used. Purple stars are CHX-A''-DTPA, orange open circles are DOTA, black filled squares are L^{py} , blue filled triangles are L^{pyd} , green open squares are L^{pyr} , and red filled circles are L^{pz} . Error bars are derived from statistical counting errors of the HPGe detector by standard error propagation calculations.

To further investigate the labeling properties of the nitrogen-rich macrocycles, the pH, temperature, and ligand concentrations were varied. Upon decreasing the ligand concentration to 10 μM (684 molar equiv to Bi) at room temperature and pH 5, the reaction kinetics were substantially slower. After 1 h, $50 \pm 5\%$ of ^{207}Bi was labeled by L^{py} , whereas <10% was complexed by the other three ligands. At 24 h, 92 ± 6 , 79 ± 6 , 69 ± 6 , and $35 \pm 4\%$ of ^{207}Bi was chelated by L^{py} , L^{pyd} , L^{pyr} , and L^{pz} , respectively, at this low ligand concentration. As expected, a 10-fold increase in the ligand concentration to 1000 μM gives rise to faster reaction kinetics, as shown in Fig. 5a. L^{py} complexes all ^{207}Bi within 5 min, and >85% is bound by the slowest ligand, L^{pz} , within 1 h. Variations in the temperature of the reaction, while maintaining ligand concentration of 100 μM and solution pH 5, also elicited changes in the kinetic profiles. At 37 °C, the labeling of L^{py} was quantitative after only five minutes (Fig. 5b). Additionally,

significant enhancements of the kinetics were observed for the other three ligands (Fig 5b). At 65 and 90 °C, labeling for all four ligands is complete within five minutes. Lastly, the effect of pH was investigated, while fixing the ligand concentration at 100 µM and the reaction temperature at 22 ± 2 °C. At pH 3, kinetics are significantly retarded. After 24 h at pH 3, only L^{py} fully complexes the ²⁰⁷Bi. For L^{pyd}, L^{pyr}, and L^{pz}, only 53 ± 5 , 44 ± 4 , and $43 \pm 3\%$, respectively, of ²⁰⁷Bi is labeled after 24 h at pH 3. Conversely, increasing the pH leads to an enhancement of the reaction kinetics. Fig. 5c shows the kinetic profile for the reaction at pH 6.8. Under these conditions quantitative labeling for all four ligands is achieved by 30 min.

Fig. 5. Radiolabeling kinetics as a function of different ligand concentration, temperature, and pH. (a) Reaction carried out using 1000 µM ligand and 3 kBq ²⁰⁷Bi. The temperature was fixed at 22 ± 2 °C and the pH at 5. (b) Reaction carried out at 37 ± 2 °C with 3 kBq ²⁰⁷Bi. The ligand concentration was 100 µM and the pH was 5. (c) Reaction carried out at pH 6.8 with 3 kBq ²⁰⁷Bi. The ligand concentration was 100 µM and the temperature was 22 ± 2 °C. Error bars are derived from statistical counting errors of the HPGe detector by standard error propagation calculations.

3.3. EDTA-challenge stability studies

To assess the stability of the radiobismuth-labeled ligands, the complexes were incubated with a large excess of EDTA. The ²⁰⁷Bi complexes, prepared from 3 kBq ²⁰⁷Bi and 100 µM ligand, were challenged with 50 mM EDTA in pH 7.4 PBS. The loss of ²⁰⁷Bi was monitored by radio-TLC, as described in Section 2.4. The stability of the complexes as a function of time is shown in Fig. 6. L^{pyr} and L^{pz} form the least stable complexes, with >50% of ²⁰⁷Bi lost after 2 days. After 7 days, CHX-A''-DTPA equilibrates with $\approx 10\%$ loss of ²⁰⁷Bi. The complex of L^{pyd} is slightly more stable under these conditions, as reflected by an approximate 6% loss of ²⁰⁷Bi.

Both L^{py} and DOTA display excellent stability to the EDTA challenge; >97% of the ^{207}Bi complexes remain intact after 7 days.

Fig. 6. Stability of ^{207}Bi -labeled complexes (100 μM ligand, 3 kBq ^{207}Bi) in the presence of 50 mM EDTA at 0.1 M PBS at pH 7.4. Purple stars are CHX-A''-DTPA, orange open circles are DOTA, black filled squares are L^{py} , blue filled triangles are L^{pyd} , green open squares are L^{pyr} , and red filled circles are L^{pz} . Error bars are derived from statistical counting errors of the HPGe detector by standard error propagation calculations.

3.4. Metal-ion competition studies

The ^{207}Bi -labeled ligands (110 μM ligand, 0.75 kBq ^{207}Bi) were challenged with a large excess (500 μM , total reaction volume 200 μL) of non-radioactive Cu^{2+} , Zn^{2+} , Fe^{3+} , and Bi^{3+} as another determinant of stability. The results are shown in Fig. 7. ^{207}Bi complexes of L^{py} , DOTA, and CHX-A''-DTPA all remain >95% intact up to 7 days when challenged with any of the four metal ions. L^{pyd} exhibits approximately 10% decomposition after 7 days in the presence of Cu^{2+} , Zn^{2+} , and Bi^{3+} . Complexes of L^{pz} are the least stable with >70% loss of ^{207}Bi when challenged with Cu^{2+} and Zn^{2+} , and $\approx 60\%$ lost when challenged with cold Bi^{3+} ions. L^{pyr} also exhibits substantial decomposition, albeit less than that for L^{pz} , when treated with the metal ions, as shown in Fig. 7. Fe^{3+} ions fail to displace any significant quantities of the ^{207}Bi for all four ligands tested.

Fig. 7. Stability of ^{207}Bi -labeled complexes (110 μM ligand, 0.75 kBq ^{207}Bi) in the presence of 0.5 mM cold (a) Cu^{2+} , (b) Zn^{2+} , (c) Fe^{3+} , and (d) Bi^{3+} in 0.1 M pH 7.4 MOPS buffer. Purple stars are CHX-A''-DTPA, orange open circles are DOTA, black filled squares are L^{py} , blue filled

triangles are L^{pyd} , green open squares are L^{pyr} , and red filled circles are L^{pz} . Error bars are derived from statistical counting errors of the HPGe detector by standard error propagation calculations.

3.5. DFT calculations

To investigate the selectivity of the ligands for Bi^{3+} over Ac^{3+} , DFT calculations were employed. The metal ion substitution reactions, shown in Fig. 8, were modeled by optimizing the geometries and calculating the free energies of all the species. Nine-coordinate hydrated ions with outer-sphere water molecules were optimized to attain energies with some degree of explicit solvation for these ions. The starting geometries for these aquated ions were taken from previously published computational studies on the hydration of lanthanides [42]. For complexes of the ligands, axial water ligands were omitted from the Bi^{3+} complexes to match the known 8-coordinate structures of this ion [38, 39]. To balance the chemical reactions, an additional water molecule was added to the outer-sphere of the hydrated La^{3+} and Ac^{3+} ions. Additionally, all of the metal complexes were optimized as the twisted square antiprismatic (TSAP) diastereomers, $\Delta(\delta\delta\delta\delta)/\Lambda(\lambda\lambda\lambda\lambda)$, where Δ/Λ indicate the helical twist of the pendant donors and δ/λ signify the chirality of each of the five-membered chelate rings. The TSAP diastereomers are thermodynamically favored for large ions [45].

The hydrated ions of Bi^{3+} , La^{3+} , and Ac^{3+} interact with 9 water molecules in the inner coordination sphere. The resulting geometries of the inner-sphere complexes for all three ions are capped twisted square antiprisms. The average inner-sphere $\text{M}-\text{OH}_2$ distances for these optimized structures are 2.537, 2.624, and 2.691 Å for Bi^{3+} , La^{3+} , and Ac^{3+} , respectively. The

distance between the axial water ligand and the metal ion is approximately 0.1 Å greater than the separation between the other water ligands. Solid-state structures, elucidated by X-ray crystallography, of the $[\text{Bi}(\text{OH}_2)_9]^{3+}$ and $[\text{La}(\text{OH}_2)_9]^{3+}$ cations reveal D_{3h} -symmetric trigonal tricapped prismatic geometries with average M–OH₂ distances of 2.54 and 2.49 Å, respectively [46-48]. Thus, the DFT calculations, which employed gas-phase optimizations, overestimate these distances, but reproduce the general trend in relative distances for Bi^{3+} and La^{3+} . Ac^{3+} with the largest ionic radius of the three ions [49] expectedly has, according to DFT calculations, the longest M–OH₂ distances. The optimized structures of the metal-ligand complexes also reflect the increase of ionic radii of the three ions. Average M–N distances for the nitrogen-rich macrocyclic compounds, which do not vary significantly depending on the ligand, are 2.64, 2.77, and 2.85 Å for Bi^{3+} , La^{3+} , and Ac^{3+} , respectively. The substantially shorter M–N distances for the Bi^{3+} complexes may arise, in part, from the lack of axial water ligand in these species.

Free energies with an implicit solvation model, for the $\text{Bi}^{3+}/\text{La}^{3+}$ and $\text{Bi}^{3+}/\text{Ac}^{3+}$ substitution reactions are given in Table 2. These results indicate that complexes of Bi^{3+} for all six ligands investigated are strongly thermodynamically favored relative to the corresponding complexes of La^{3+} and Ac^{3+} . Ac^{3+} complexes are systematically destabilized relative to those of La^{3+} as well. Notably, the nitrogen-rich macrocycles strongly prefer Bi^{3+} to La^{3+} and Ac^{3+} ; the free energy difference for this substitution reaction is much greater than for that with DOTA and CHX-DTPA.

Fig. 8. Reaction schemes used to calculate metal-ion substitution energies with DFT. Results are shown in Table 2. Note that overall complex charges for DOTA and CHX-DTPA are –1 and –2, respectively.

Table 2. Free Energies (kJ/mol) Calculated by DFT for the Metal-Ion Exchange Reactions Shown in Fig. 8

	L^{py}	L^{pyd}	L^{pyr}	L^{pz}	DOTA	CHX-DTPA
La^{3+}	172.1	137.8	161.2	152.8	97.5	98.9
Ac^{3+}	267.7	230.0	241.9	240.9	164.5	163.4

To probe directly the relative thermodynamic selectivity of the nitrogen-rich macrocycles, DOTA, and CHX-DTPA for Bi^{3+} , the free energies for the reactions shown in Fig. 9 were computed. These reaction schemes avoid use of the free aquated metal ions, and therefore circumvent the associated errors in calculating the relative energies of such species [50]. Table 3 collects the free energies of the reactions in Fig. 9. The substitution of La^{3+} or Ac^{3+} in DOTA for Bi^{3+} in the nitrogen-rich macrocycles is strongly disfavored. These energies indicate that the nitrogen-rich macrocycles are highly selective for Bi^{3+} in comparison to DOTA. The polyamino carboxylate CHX-DTPA fails to exhibit thermodynamic selectivity over DOTA. The free energies changes for the reactions involving these two ligands are close to zero.

Fig. 9. Reaction schemes used to calculate the relative selectivity of ligands, compared to DOTA, for Bi^{3+} . Results are shown in Table 3.

Table 3. Free Energies (kJ/mol) Calculated by DFT for Reactions Shown in Fig. 9

	L^{py}	L^{pyd}	L^{pyr}	L^{pz}	CHX-DTPA
La^{3+}	74.6	40.3	63.7	55.3	1.4
Ac^{3+}	103.3	65.5	77.4	76.5	-1.1

To investigate the origin of this selectivity, the strain energy of the ligands was calculated. The strain energy is the energy of the ligand at the conformation in the optimized structures of the metal complexes. Table 4 contains the relative strain energies of the ligands computed from single-point energy calculations of ligand geometries in the metal complexes. For all ligands, complexes of Ac^{3+} give rise to the smallest strain energies, which are normalized to zero. Bi^{3+} complexes require the largest strain energies. Strain energies show little dependence on the ligand. The exception is L^{pyd} , which exhibits substantially larger strain energy in the Bi^{3+} complex compared to the other ligands.

Table 4. Relative Strain Energies (kJ/mol)^a of Ligands in Metal Complexes

	L^{py}	L^{pyd}	L^{pyr}	L^{pz}	DOTA	CHX-DTPA
Ac^{3+}	0	0	0	0	0	0
La^{3+}	14.8	14.3	14.2	14.9	11.7	14.5
Bi^{3+}	31.7	64.1	31.3	31.7	22.9	28.2

^a Normalized to Ac^{3+} complexes, which exhibit the lowest ligand strain energies

4. Discussion

The design of bifunctional chelating agents that form strong complexes with ^{213}Bi has been the focus of many synthetic efforts. A number of multi-dentate polyamino carboxylate ligands for Bi^{3+} chelation have been synthesized and characterized [51-60]. In particular, the polyamino carboxylate ligands known as DEPA and NETA exhibit fast Bi^{3+} -labeling kinetics and high stability, making them among the best known ligands for this unique ion [55, 58, 59, 61]. Other researchers have also begun to explore the use of porphyrins and texaphyrins for the stable chelation of radiobismuth [62-65]. Despite these vast synthetic endeavors, most biological and preclinical studies still employ DOTA [21, 66, 67] or CHX-A''-DTPA [68, 69], which are favorable because of their commercial availability and broad utilization for a variety of established radiopharmaceutical applications.

Non-radioactive Bi^{3+} complexes of L^{py} , which possess in vitro anticancer activity [70], have previously been reported and characterized [38]. Although proposed for use in ^{213}Bi TAT, these ligands were not further pursued due to their reportedly low water solubility [38]. In our hands, L^{py} exhibits good solubility in pH 5 NH_4OAc buffer, an effect that can most likely be attributed to either the increase ionic strength of the buffer solution or the slightly acidic pH. In this study, we were initially interested in exploring the coordination chemistry of L^{py} and newly prepared analogues with ^{225}Ac . Unexpectedly, we found that all four macrocyclic ligands selectively chelate Bi^{3+} over Ac^{3+} (Table 1). This behavior is in contrast to DOTA, currently the chelator of choice for ^{225}Ac [71, 72], and CHX-A''-DTPA, which both inevitably bind ^{225}Ac . Because breakthrough of ^{225}Ac from $^{225}\text{Ac}/^{213}\text{Bi}$ generator systems is a possible concern [73], especially given the potential for human error, ligands with high selectivity for Bi^{3+} over Ac^{3+}

may be valuable in mitigating the effects of such incidents by minimizing undesired patient exposure to longer-lived ^{225}Ac .

Prompted by the unique Bi^{3+} -selective labeling properties of these ligands, we further investigated their potentials for use in ^{213}Bi TAT. Radiolabeling kinetic experiments reveal that L^{py} complexes Bi^{3+} faster than DOTA, but more slowly than CHX-A''-DTPA (Fig. 4). The rapid binding kinetics of CHX-A''-DTPA are expected based on its acyclic structure [74]. Many ^{213}Bi constructs utilize DOTA with great efficacy [21, 66, 67]. Therefore, the observation that L^{py} binds to Bi^{3+} more rapidly than DOTA bodes well for its potential use in ^{213}Bi chelation. Surprisingly, the Bi^{3+} -labeling kinetics of the other three ligands varies substantially depending on the nature of the pendant *N*-heterocycle. The order for binding kinetics follows $\text{L}^{\text{py}} > \text{L}^{\text{pyd}} > \text{L}^{\text{pyr}} > \text{L}^{\text{pz}}$. Notably, this sequence follows the pK_{a} values of the pendant *N*-heterocycle. Pyridine is the most basic (conjugate acid pK_{a} 5.23) and pyrazine is the least basic (conjugate acid pK_{a} 0.65); the corresponding values for pyridazine and pyrimidine are 2.33 and 1.30, respectively. This correlation suggests that analogous ligands with more basic pendant donors, like imidazole, should be investigated for Bi^{3+} chelation.

The solution pH, temperature, and ligand concentrations were varied to investigate their role in Bi^{3+} radiolabeling kinetics (Fig. 5). Using only 10 μM ligand ($\text{L}:\text{}^{207}\text{Bi}$ molar ratio 690) at pH 5 and room temperature gives rise to substantially slower binding kinetics; only 50% of ^{207}Bi is complexed by L^{py} and < 10% by the three other ligands after 60 min. Conversely, the use of 1000 μM ligand ($\text{L}:\text{}^{207}\text{Bi}$ molar ratio of 69,000) increases complexation kinetics. Increases in temperature also predictably accelerate labeling kinetics. Holding the ligand concentration at 100 μM and the reaction pH at 5, increasing the temperature to 37 $^{\circ}\text{C}$, a temperature that is compatible for antibody labeling, gave substantially improved radiolabeling kinetics. After 5

min, > 90% of ^{207}Bi was labeled with L^{py} . After 1 h, L^{pyd} and L^{pyr} were quantitatively labeled, and >70% labeling was achieved with L^{pz} . At 65 and 90 °C, labeling was 100% for all ligands after 5 min. The role of pH was also probed. At pH 3 with 100 μM ligand and at room temperature, kinetics were substantially impeded. This rate decrease at low pH most likely arises due to protonation of the ligand, which decreases the available concentration of the metal-binding deprotonated form. At pH 6.8, only a 5 min time period is required to label 100% of ^{207}Bi with L^{py} and 30 min for the other three ligands. The decrease in competing H^+ ions at this higher pH gives rise to acceleration of the labeling. The three variables, pH, temperature, and concentration, investigated here reveal that there are possible strategies for increasing specific activities of the radiolabeled constructs. For short-lived ^{213}Bi , the physical decay of this isotope will also provide another challenge in achieving high specific activities. In the absence of temperature-sensitive antibodies, a clear radiolabeling strategy is to use low ligand concentration, neutral pH, and high temperatures for labeling.

In addition to possessing rapid radiolabeling kinetics, the overall stability of the labeled ligands must be high in order to avoid loss of the radioisotope in vivo. To test the stability of the nitrogen-rich macrocycles, the ^{207}Bi -labeled ligands (100 μM ligand, 3 kBq ^{207}Bi , molar ratio 6900) were challenged with 50 mM EDTA at pH 7.4. The results, shown in Fig. 6, reveal that both L^{pz} and L^{pyr} exhibit poor stability over several days. In contrast, L^{py} and L^{pyd} retain ^{207}Bi effectively with less than 3% loss for L^{py} and approximately 6% loss for L^{pyd} after 7 days. These values are an improvement to CHX-A''-DTPA where 10% loss of ^{207}Bi is observed over the same time period. The ^{207}Bi -DOTA complex is equally stable to that of L^{py} . The value of L^{py} as a chelating agent for Bi^{3+} is therefore reflected by the observations that its labeling kinetics are substantially enhanced relative to DOTA, yet it forms equally stable complexes. The therapeutic

isotope, ^{213}Bi , only has a 46-min half-life, and therefore the multi-day stability challenges presented out here are not directly relevant to its use. However, this long-term stability can be used to extrapolate the relative stabilities of the species in vivo, where much more challenging conditions are present.

The stability was further probed by challenging the complexes with an excess of non-radioactive metal ions, which can potentially compete with the radiobismuth for ligand-binding. Cu^{2+} and Zn^{2+} were chosen because these ions are present in blood plasma. Fe^{3+} is also present in vivo, and is one of the major metallic contaminants found in reagents and solutions used for radiolabeling. The use of cold Bi^{3+} for a stability challenge enables a direct probe of the ligand exchange kinetics without complicating factors caused by different thermodynamic affinities for the different metal ions. The metal ions were present in a five-fold excess relative to the ligands, whereas the molar ratio of cold metal ions to ^{207}Bi is $>10^5$. The results shown in Fig. 7 are largely consistent with those from the EDTA-challenge stability study; L^{pz} and L^{pyr} form the least stable complexes. The stability of L^{py} is further verified by these studies as well, where the complex remains 100% intact against any of the offending metals up to seven days. This stability matches those observed for DOTA and CHX-A''-DTPA. In comparing the efficacy of the competing metal ions, it is noteworthy that Fe^{3+} fails to eject ^{207}Bi from any ligand. This stability in the presence of Fe^{3+} is valuable because of the ubiquitous presence of this ion both in biology and as a contaminant in standard reagents. In contrast, Cu^{2+} and Zn^{2+} are able to effectively displace ^{207}Bi from L^{pyr} and L^{pz} ; this observation may indicate a higher affinity of these ligands for Cu^{2+} and Zn^{2+} than Fe^{3+} . The replacement of ^{207}Bi with cold Bi^{3+} is a good indication of the kinetic inertness of the ligands tested, because this exchange is thermoneutral. The low kinetic stability of L^{pyr} and L^{pz} is revealed by a loss of radioactivity within the ligands. For L^{py} , DOTA,

and CHX-A''-DTPA, however, no exchange with cold Bi^{3+} is observed over the course of 7 days signifying the kinetic inertness of radiolabeled complex. These studies further validate the stability of L^{py} , indicating that it performs equally well as DOTA and CHX-A''-DTPA against these challenges.

A novel feature of the ligands investigated here is their strong selectivity and affinity for Bi^{3+} . Using the three-parameter equation of Hancock and Martell [75, 76], $\log K$, where K is the thermodynamic stability constant, for NH_3 can be predicted for any metal ion if the corresponding values for F^- and OH^- are known. The predicted $\log K$ for NH_3 of the Bi^{3+} ion is 5.1, suggesting a surprisingly high affinity of this ion for nitrogen donors. The high nitrogen affinity of Bi^{3+} was further verified by polarographic stability constant measurements and structural studies of this ion with multi-dentate nitrogen-donor ligands [77-80]. In contrast, the predicted $\log K$ for NH_3 of Ac^{3+} , using reported values for F^- [81] and OH^- [82], is only 0.8. Therefore, one factor dictating the selectivity of the ligands investigated here is the nitrogen-rich donor set that they provide, which is strongly preferred by the Bi^{3+} ion. An additional factor that can contribute to the observed selectivity is the difference in ionic radii of Bi^{3+} and Ac^{3+} . Ac^{3+} is the largest +3 ion known; its 6-coordinate ionic radius is 1.12 Å [49]. For Bi^{3+} , this value is 1.03 Å [49], although a revised radius of 0.99 Å has been suggested [48]. The ligand framework of L^{py} and analogues may not be able to satisfactorily accommodate the large Ac^{3+} ion.

DFT calculations were carried out to investigate and confirm experimental findings regarding the selectivity of these ligands for Bi^{3+} over Ac^{3+} . Complexes of La^{3+} were also investigated because they possess a similar six-coordinate ionic radius to Bi^{3+} (1.03 Å) and have a similarly low affinity for nitrogen-donor ligands as Ac^{3+} ($\log K \text{ NH}_3 = 0.2$, estimated from the same three-parameter equation). These La^{3+} complexes can therefore potentially be utilized to

disentangle size effects from donor-atom preferences. Optimized structures of the hydrated ions metal-ligand complexes revealed that those of Bi^{3+} ion contained the shortest metal-ligand interactions of the series. For the nonaqua ions, the average $\text{Bi}-\text{OH}_2$ inner-sphere distance is 2.537 Å, compared to 2.624 and 2.691 Å for La^{3+} and Ac^{3+} , respectively. For the nitrogen-rich macrocycles, average M–N distances follow the same order; these values are 2.64, 2.77, and 2.85 Å for complexes of Bi^{3+} , La^{3+} , and Ac^{3+} , respectively. The increased M–L distances for Ac^{3+} complexes relative to those of La^{3+} are expected based on its larger ionic radius. The large increase in M–L distances, however, in moving from Bi^{3+} to La^{3+} is somewhat surprising. Notably, this deviation is observed experimentally by X-ray crystallography where the average M– OH_2 distance for the nonaqua ions of La^{3+} is 0.053 Å greater than that of Bi^{3+} [46, 47], and the average M–N distance for the L^{py} complex of La^{3+} is 0.116 Å greater than that of Bi^{3+} . The proposed revised six-coordinate ionic radius of Bi^{3+} of 0.99 Å [48], which is only slightly smaller than the originally suggested value and the ionic radius of La^{3+} , may partially account for the observed contraction. Additionally, the stereoactive $6s^2$ lone-pair of Bi^{3+} , which occupies a coordination site, most likely plays an important role as well.

The computed energies of metal ion substitution are given in Table 2. Substitution of Bi^{3+} for La^{3+} is strongly favored thermodynamically. The analogous substitution for Ac^{3+} is even more greatly favored by up to another 100 kJ/mol. The thermodynamic penalty for replacing La^{3+} with Bi^{3+} in DOTA is expected based on the known stability constants of these ions with DOTA. The reported stability constants ($\log K$) for $[\text{La}(\text{DOTA})]^{1-}$ at 25 °C range from 21.7 to 24.25 [83-85], whereas the stability constant for $[\text{Bi}(\text{DOTA})]^{1-}$ is 30.3 [39]. This difference in $\log K$ values (8.6) maximally corresponds to a free energy difference of 49 kJ/mol, a value smaller than that computed with DFT. For CHX-A''-DTPA the $\log K$ for Bi^{3+} is 34.9 [86]; values

for La^{3+} are not reported. Importantly, the nitrogen-rich macrocycles favor Bi^{3+} coordination relative to Ac^{3+} by up to 100 kJ/mol more than DOTA and CHX-A''-DTPA. This result can manifest maximally in a difference of stability constants of 17 logarithmic units.

Although these values qualitatively show the expected trends the absolute values should be interpreted with caution due to the large deviation between computation and experimental results for DOTA binding affinity. This deviation from experimental results most likely arises from the difficulty in accurately computing the energies of aquated ions [50], which may exist in different protonation states and ion pairs in a pH- and electrolyte-dependent manner. Hence the selectivity of the nitrogen-rich macrocycles for Bi^{3+} was computed in comparison to DOTA with the reaction schemes shown in Fig. 9, which do not require energy terms for the aquated ions. The values in Table 3 clearly support the strong selectivity of the nitrogen-rich macrocycles for Bi^{3+} in comparison to DOTA. These values indicate that neither Ac^{3+} nor La^{3+} can effectively compete with Bi^{3+} for these ligands. In contrast, CHX-DTPA shows no strong metal-binding preference in comparison to DOTA, highlighting the novel selective properties of the nitrogen-rich macrocycles. The computed results that coordination to La^{3+} is *less* disfavored than to Ac^{3+} suggests that size of the ion also plays a role. The nitrogen affinity of these two ions is nearly identical, and therefore the larger size of Ac^{3+} is presumably the major factor in the almost 100 kJ/mol free energy difference between coordination of the two ions. This observation highlights the continuing challenge in the development of chelating agents for Ac^{3+} [72, 87], as conventional macrocyclic scaffolds, including DOTA, cannot optimally interact with this large ion. Somewhat paradoxically, ligand strain energies follow the opposite trend in overall metal-complex stability. Strain energies (Table 4) are smallest for Ac^{3+} and largest for Bi^{3+} . Presumably the large Ac^{3+} ion maintains the ligand in an open relaxed state due to Pauli

repulsion, a steric effect of the large ion. The major consequence of this small ligand strain, however, is the decreased opportunity for orbital overlap, an effect which most likely contributes to the high stability of the Bi^{3+} complexes.

5. Conclusions

The nitrogen-rich macrocyclic ligands investigated in this work have a strong selectivity for Bi^{3+} over Ac^{3+} . This selectivity is important to minimize detrimental effects of $^{225}\text{Ac}/^{213}\text{Bi}$ generator breakthrough that can lead to inadvertent patient dosing with small quantities of long-lived ^{225}Ac . DFT calculations indicate that coordination of these ligand to either La^{3+} or Ac^{3+} is strongly disfavored thermodynamically relative to Bi^{3+} . This thermodynamic preference most likely arises from the high affinity of Bi^{3+} for nitrogen donors. Hence, the use of nitrogen-rich ligands represents a strategy for designing stable and selective Bi^{3+} chelating agents.

Furthermore, significant differences between the radiolabeling kinetics and stability of the four ligands investigated reveal that subtle electronic differences can manifest in the utility of these ligands for Bi^{3+} chelation. Therefore, appropriate modification of these electronic parameters can potentially lead to improved ligands for Bi^{3+} . The best candidate for Bi^{3+} chelation, L^{py} , exhibits faster kinetics and equal stability to EDTA and cold metal ion competition reactions as DOTA. The synthesis of a bifunctional analog of L^{py} and further evaluation of its utility for ^{213}Bi TAT are in progress. Additional efforts are also aimed at using similar rational design principles for the development of an appropriate chelator for ^{225}Ac , work which may possibly stimulate further interest in the use of this isotope for therapeutic applications. Controlling the α -emitting daughters of ^{225}Ac in vivo, however, presents a formidable challenge that requires creative approaches beyond conventional ligand design strategies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:XXXXXXXXX.

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Supplementary Data for

Evaluation of Nitrogen-Rich Macrocyclic Ligands for the Chelation of Therapeutic Bismuth Radioisotopes

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Table S1. DFT-optimized Cartesian coordinates and energies for $[\text{Bi}(\text{OH}_2)_9](\text{OH}_2)_{11}^{3+}$

O	1.237100	-2.154500	0.023500
H	1.326700	-2.665300	-0.809200
H	1.960900	-2.401400	0.647100
O	-1.194400	-1.761000	-1.425000
H	-1.782200	-2.442300	-1.012300
H	-0.536500	-2.244900	-1.979800
O	1.188600	-0.154700	-1.913500
H	2.132500	-0.427100	-1.793300
H	1.258300	0.663700	-2.449000
O	-2.612200	0.346800	-0.411600
H	-3.120600	1.042800	0.070200
H	-3.244900	-0.225300	-0.896900
O	-0.407300	2.060100	-0.982200
H	0.350700	2.696800	-0.965800
H	-1.222300	2.576100	-1.161800
O	0.838900	-0.938400	2.559100
H	0.854600	-0.174600	3.188200
H	0.085000	-1.507600	2.807800
O	1.815400	1.304300	0.953800
H	2.689800	0.835500	1.008800
H	1.981900	2.108000	0.393200
O	-1.621500	-1.617200	1.635000
H	-2.162200	-0.950900	2.098500
H	-2.239200	-2.271700	1.215300
O	-1.325600	1.111500	2.012100
H	-0.712700	1.473500	2.698300
H	-2.003300	1.796600	1.795600
O	3.931000	-0.267500	-1.779200
H	4.227700	-0.200700	-0.836400
H	4.571700	-0.839300	-2.234000

O	-4.688200	-1.414500	-1.368100
H	-4.775800	-1.619600	-2.316100
H	-5.594000	-1.209900	-1.073900
H	-3.851100	-2.735100	-0.443000
O	-3.066400	-3.176700	-0.037900
H	-3.277900	-4.119800	0.070000
O	1.969800	3.336700	-0.834200
H	2.402000	2.998500	-1.668000
H	2.250300	4.257300	-0.700400
O	-2.574400	3.956100	-1.210000
H	-3.179000	3.955600	-1.973300
H	-2.283700	4.881700	-1.126800
H	-3.262800	3.233700	0.300100
O	-3.421600	2.532200	0.975500
H	-4.211900	2.783800	1.482700
O	2.778500	1.945100	-2.940500
H	3.046900	2.308600	-3.801300
H	3.469700	1.297600	-2.666800
O	4.219900	-0.053300	0.926700
H	4.031400	-0.924100	1.367600
H	5.017100	0.311700	1.348400
O	0.845300	1.575300	3.527200
H	1.425600	1.815300	2.771200
H	1.120700	2.076200	4.313400
O	3.129700	-2.277700	1.987800
H	2.411000	-1.895900	2.546000
H	3.527300	-3.022400	2.471200
O	0.865700	-3.243100	-2.536800
H	1.280900	-2.845400	-3.320900
H	0.769400	-4.189200	-2.745400
Bi	-0.240900	-0.157500	0.121500

Zero-point correction=	0.514514 (Hartree/Particle)
Thermal correction to Energy=	0.562458
Thermal correction to Enthalpy=	0.563402
Thermal correction to Gibbs Free Energy=	0.436787
Sum of electronic and zero-point Energies=	-1532.704093
Sum of electronic and thermal Energies=	-1532.656149
Sum of electronic and thermal Enthalpies=	-1532.655205
Sum of electronic and thermal Free Energies=	-1532.781821

E(SCF) in SMD Solvation Model= -1533.69815425

Table S2. DFT-optimized Cartesian coordinates and energies for $[\text{La}(\text{OH}_2)_9](\text{OH}_2)_{12}^{3+}$

La	-0.171500	-0.071700	-0.063300
O	1.142500	-2.249300	-0.392600
H	1.290600	-2.599600	-1.298100
H	1.582700	-2.831600	0.269100
O	-1.014500	-1.214600	-2.140900
H	-1.799100	-1.817600	-2.101400
H	-0.338200	-1.665800	-2.701200
O	1.842100	0.046700	-1.824400
H	2.662800	-0.423600	-1.530400
H	2.187600	0.916300	-2.117000
O	-2.348500	1.038700	-0.829400
H	-2.714800	1.780100	-0.292100
H	-3.120500	0.542100	-1.188600
O	0.342400	2.355700	-0.665800
H	1.177100	2.784100	-0.349900
H	-0.254800	3.072900	-0.974400
O	0.147500	-1.531300	2.255200
H	0.170800	-0.929800	3.042900
H	-0.746900	-1.928700	2.202300
O	1.942200	0.703600	1.487300
H	2.695000	0.062000	1.583000
H	2.351400	1.557000	1.181600
O	-2.134900	-1.708300	0.776900
H	-2.961700	-1.334500	1.156100
H	-2.452900	-2.337000	0.081900
O	-1.284200	1.155600	1.889400
H	-0.821400	1.206800	2.757700
H	-1.750600	2.006700	1.716700
O	4.392700	-0.665700	-1.071800
H	4.427300	-0.890800	-0.108500
H	5.010600	-1.265900	-1.521800
O	-4.663700	-0.486100	-1.315400
H	-5.413800	-0.213300	-1.871200
H	-5.000300	-0.586400	-0.394700
H	-3.905000	-2.071100	-1.635100
O	-3.177000	-2.731900	-1.525200
H	-3.467500	-3.572300	-1.917500
O	2.801200	2.981300	0.287800
H	3.380700	2.736200	-0.487400
H	3.172100	3.781100	0.696400
O	-1.363600	4.581600	-1.148000
H	-1.853600	4.648600	-1.986700
H	-0.976200	5.464700	-1.012800
H	-2.335000	3.884500	0.224100
O	-2.765900	3.208800	0.798800

H	-3.547700	3.630700	1.192400
O	3.953500	1.930600	-1.862000
H	4.509700	2.404400	-2.503200
H	4.435400	1.109600	-1.605600
O	3.993900	-1.134300	1.595800
H	3.538200	-2.001100	1.764500
H	4.715800	-1.063800	2.244000
O	-4.874800	-1.061900	1.392500
H	-5.198100	-0.424000	2.052400
H	-5.349000	-1.887200	1.599900
O	0.489300	0.622200	3.844200
H	1.255500	0.867700	3.279700
H	0.699900	0.830900	4.769800
O	2.289300	-3.218700	1.872600
H	1.511300	-2.812200	2.320200
H	2.424900	-4.106300	2.246400
O	1.229900	-2.370100	-3.164300
H	1.686600	-1.523200	-3.322000
H	1.383800	-2.936400	-3.939800

Zero-point correction=	0.539820 (Hartree/Particle)
Thermal correction to Energy=	0.590165
Thermal correction to Enthalpy=	0.591110
Thermal correction to Gibbs Free Energy=	0.460008
Sum of electronic and zero-point Energies=	-2039.616754
Sum of electronic and thermal Energies=	-2039.566408
Sum of electronic and thermal Enthalpies=	-2039.565464
Sum of electronic and thermal Free Energies=	-2039.696566

E(SCF) in SMD Solvation Model= -2040.66400091

Table S3. DFT-optimized Cartesian coordinates and energies for $[\text{Ac}(\text{OH}_2)_9](\text{OH}_2)_{12}^{3+}$

Ac	-0.106900	-0.022500	-0.071700
O	1.148500	-2.359200	-0.212000
H	1.319600	-2.790300	-1.077900
H	1.632100	-2.838600	0.499900
O	-0.871600	-1.376400	-2.182100
H	-1.666900	-1.961900	-2.131400
H	-0.180400	-1.892400	-2.655200
O	1.945300	-0.037700	-1.801400
H	2.763100	-0.500800	-1.497400
H	2.300600	0.795600	-2.174800
O	-2.391300	1.014700	-0.944500
H	-2.764600	1.794300	-0.469900

H	-3.154300	0.494800	-1.289100
O	0.388300	2.463900	-0.803900
H	1.236200	2.886000	-0.513400
H	-0.199000	3.180400	-1.132500
O	0.111200	-1.341300	2.421500
H	0.027800	-0.717300	3.183200
H	-0.747900	-1.802000	2.323400
O	1.985800	0.817700	1.372400
H	2.744900	0.225300	1.598700
H	2.386300	1.674100	1.077700
O	-2.119300	-1.732200	0.830700
H	-2.981100	-1.380600	1.146900
H	-2.375400	-2.386900	0.136100
O	-1.326300	1.371000	1.844900
H	-0.986900	1.434700	2.763300
H	-1.820600	2.191400	1.615300
O	4.503200	-0.697900	-0.959100
H	4.513700	-0.841300	0.019700
H	5.162500	-1.304000	-1.336000
O	-4.633800	-0.619200	-1.433500
H	-5.374200	-0.401100	-2.025300
H	-4.998300	-0.707300	-0.522700
H	-3.795300	-2.182800	-1.657800
O	-3.070400	-2.838800	-1.506000
H	-3.362800	-3.694200	-1.862400
O	2.865200	3.083700	0.110200
H	3.448400	2.778100	-0.638300
H	3.250800	3.896400	0.476800
O	-1.367500	4.613500	-1.405300
H	-1.795700	4.624200	-2.279800
H	-1.019900	5.514900	-1.283200
H	-2.393200	3.936500	-0.057000
O	-2.839800	3.292200	0.542100
H	-3.643600	3.728000	0.871000
O	4.051100	1.852600	-1.944700
H	4.620400	2.271900	-2.611600
H	4.524500	1.052800	-1.617600
O	4.077500	-0.962700	1.750200
H	3.613200	-1.805700	1.986000
H	4.787600	-0.837200	2.402700
O	-4.905800	-1.117700	1.294300
H	-5.258100	-0.445200	1.902800
H	-5.384200	-1.933600	1.527900
O	-0.125600	0.738000	4.278900
H	0.725100	1.171200	4.465600

H	-0.579800	0.678300	5.138100
O	2.318600	-3.009800	2.166000
H	1.536100	-2.560000	2.560000
H	2.446600	-3.852100	2.634900
O	1.249400	-3.031400	-2.948600
H	1.892100	-2.566800	-3.511200
H	1.123800	-3.902900	-3.363200

Zero-point correction=	0.537141 (Hartree/Particle)
Thermal correction to Energy=	0.589252
Thermal correction to Enthalpy=	0.590196
Thermal correction to Gibbs Free Energy=	0.453429
Sum of electronic and zero-point Energies=	-1979.705819
Sum of electronic and thermal Energies=	-1979.653708
Sum of electronic and thermal Enthalpies=	-1979.652764
Sum of electronic and thermal Free Energies=	-1979.789531

E(SCF) in SMD Solvation Model= -1980.78691714

Table S4. DFT-optimized Cartesian coordinates and energies for $[\text{Bi}(\text{L}^{\text{py}})]^{3+}$

C	1.250100	1.859200	2.807600
H	1.998700	2.534700	3.245000
H	0.940900	1.187600	3.611800
C	0.064100	2.691800	2.327400
H	-0.320700	3.276400	3.174300
H	0.387500	3.413500	1.574500
C	-1.859300	1.250400	2.807500
H	-2.534800	1.999000	3.244800
H	-1.187600	0.941300	3.611800
C	-2.691800	0.064300	2.327500
H	-3.276300	-0.320500	3.174600
H	-3.413700	0.387500	1.574700
C	-1.250300	-1.859000	2.807800
H	-1.998900	-2.534300	3.245200
H	-0.941100	-1.187200	3.611900
C	-0.064300	-2.691700	2.327800
H	0.320600	-3.276000	3.174900
H	-0.387600	-3.413700	1.575200
C	1.859000	-1.250200	2.807700
H	1.187400	-0.941100	3.611900
H	2.534500	-1.998800	3.245000
C	2.691700	-0.064200	2.327800
H	3.276000	0.320600	3.174900
H	3.413600	-0.387500	1.575100

C	2.737000	1.885200	0.866900
H	3.602100	2.243900	1.440900
H	2.161800	2.769700	0.575200
C	3.211400	1.177000	-0.385700
C	4.467700	1.453900	-0.927100
H	5.138700	2.141700	-0.421700
C	4.847500	0.839400	-2.121700
H	5.819800	1.044300	-2.559600
C	3.960700	-0.046800	-2.735300
H	4.215500	-0.550200	-3.661900
C	2.732800	-0.285300	-2.126100
H	2.021900	-0.979300	-2.563100
C	-1.885300	2.736800	0.866500
H	-2.244300	3.601900	1.440300
H	-2.769600	2.161300	0.574700
C	-1.177000	3.211100	-0.386200
C	-1.453800	4.467400	-0.927700
H	-2.141500	5.138500	-0.422200
C	-0.839400	4.847000	-2.122400
H	-1.044200	5.819200	-2.560300
C	0.046700	3.960100	-2.735900
H	0.550100	4.214700	-3.662700
C	0.285200	2.732200	-2.126600
H	0.979100	2.021300	-2.563500
C	-2.736700	-1.885300	0.866700
H	-3.601600	-2.244600	1.440500
H	-2.160900	-2.769300	0.574700
C	-3.211300	-1.177000	-0.385800
C	-4.467700	-1.453800	-0.927100
H	-5.138700	-2.141500	-0.421500
C	-4.847400	-0.839400	-2.121800
H	-5.819700	-1.044300	-2.559500
C	-3.960500	0.046600	-2.735500
H	-4.215300	0.549900	-3.662200
C	-2.732500	0.285000	-2.126400
H	-2.021700	0.978900	-2.563500
C	1.885100	-2.736800	0.866700
H	2.244100	-3.601900	1.440500
H	2.769300	-2.161200	0.574900
C	1.176900	-3.211200	-0.386000
C	1.454100	-4.467300	-0.927700
H	2.142000	-5.138300	-0.422400
C	0.839800	-4.846800	-2.122500
H	1.045000	-5.818800	-2.560600
C	-0.046500	-3.960000	-2.736000

H	-0.549800	-4.214600	-3.662700
C	-0.285400	-2.732300	-2.126400
H	-0.979500	-2.021400	-2.563300
N	1.871200	1.033500	1.731800
N	-1.033600	1.871200	1.731500
N	-1.871200	-1.033400	1.731700
N	1.033400	-1.871200	1.731700
N	2.356400	0.312700	-0.975900
N	-0.312800	2.356100	-0.976300
N	-2.356300	-0.312800	-0.976100
N	0.312400	-2.356200	-0.976000
Bi	-0.000000	-0.000000	0.196100

Zero-point correction=	0.698458 (Hartree/Particle)
Thermal correction to Energy=	0.733338
Thermal correction to Enthalpy=	0.734282
Thermal correction to Gibbs Free Energy=	0.633910
Sum of electronic and zero-point Energies=	-1685.392680
Sum of electronic and thermal Energies=	-1685.357800
Sum of electronic and thermal Enthalpies=	-1685.356856
Sum of electronic and thermal Free Energies=	-1685.457228

E(SCF) in SMD Solvation Model= -1686.53916617

Table S5. DFT-optimized Cartesian coordinates and energies for [Bi(L^{pyd})]³⁺

C	1.923500	-1.162600	2.833700
H	2.637500	-1.868500	3.281200
H	1.232800	-0.884300	3.632900
C	2.696300	0.066300	2.353500
H	3.267200	0.470600	3.201000
H	3.429500	-0.223400	1.597700
C	1.162000	1.922800	2.834300
H	1.867600	2.636500	3.282700
H	0.882700	1.231800	3.633000
C	-0.066500	2.695900	2.353700
H	-0.471300	3.266200	3.201400
H	0.223300	3.429900	1.598600
C	-1.922500	1.161600	2.833800
H	-2.636200	1.867100	3.282400
H	-1.231600	0.882400	3.632400
C	-2.695700	-0.066900	2.353300
H	-3.266400	-0.471500	3.200800
H	-3.429100	0.223000	1.597800
C	-1.161500	-1.924200	2.833300

H	-0.882400	-1.234000	3.632700
H	-1.867200	-2.638300	3.281000
C	0.067000	-2.696900	2.351900
H	0.471900	-3.268500	3.198700
H	-0.223300	-3.429400	1.595800
C	2.023500	-2.666400	0.904100
H	2.361100	-3.556100	1.454900
H	2.920500	-2.086000	0.665900
C	1.374600	-3.084600	-0.400400
C	1.790500	-4.224700	-1.105900
H	2.566600	-4.872800	-0.709300
C	1.175500	-4.484300	-2.317500
H	1.446100	-5.344100	-2.922300
C	0.169400	-3.599400	-2.741600
H	-0.359400	-3.746000	-3.678600
C	2.667300	2.022500	0.906900
H	3.556400	2.360000	1.458600
H	2.087700	2.920000	0.668300
C	3.087900	1.373400	-0.396800
C	4.228500	1.790100	-1.100900
H	4.876000	2.566300	-0.703300
C	4.489600	1.176000	-2.312600
H	5.349900	1.447200	-2.916400
C	3.605400	0.169900	-2.738100
H	3.752900	-0.358100	-3.675400
C	-2.021800	2.667100	0.905800
H	-2.358200	3.557300	1.456500
H	-2.919900	2.088300	0.667700
C	-1.372700	3.085300	-0.398600
C	-1.788500	4.225600	-1.103900
H	-2.563600	4.874500	-0.706600
C	-1.174800	4.484400	-2.316300
H	-1.445600	5.344300	-2.921000
C	-0.169900	3.598800	-2.741200
H	0.358100	3.744700	-3.678800
C	-2.667900	-2.022700	0.906000
H	-3.556800	-2.360300	1.457900
H	-2.088400	-2.919900	0.666300
C	-3.088500	-1.372600	-0.397200
C	-4.231200	-1.786100	-1.099900
H	-4.880200	-2.560600	-0.701600
C	-4.492100	-1.171100	-2.311200
H	-5.353900	-1.440100	-2.914000
C	-3.606200	-0.167000	-2.737500
H	-3.753700	0.361900	-3.674400

N	1.134500	-1.833000	1.761000
N	1.833100	1.134000	1.762300
N	-1.133800	1.832800	1.761600
N	-1.832800	-1.134800	1.761500
N	0.404300	-2.296500	-0.875800
N	2.300700	0.402800	-0.873400
N	-0.403600	2.296000	-0.875100
N	-2.299200	-0.404300	-0.874800
N	0.210000	2.537800	-2.034200
N	-2.542900	0.211100	-2.032600
N	-0.210500	-2.538600	-2.034300
N	2.544100	-0.211000	-2.032000
Bi	-0.000400	-0.000500	0.205500

Zero-point correction=	0.647705 (Hartree/Particle)
Thermal correction to Energy=	0.682307
Thermal correction to Enthalpy=	0.683251
Thermal correction to Gibbs Free Energy=	0.583388
Sum of electronic and zero-point Energies=	-1749.460747
Sum of electronic and thermal Energies=	-1749.426146
Sum of electronic and thermal Enthalpies=	-1749.425201
Sum of electronic and thermal Free Energies=	-1749.525064

E(SCF) in SMD Solvation Model= -1750.56391571

Table S6. DFT-optimized Cartesian coordinates and energies for $[\text{Bi}(\text{L}^{\text{pyr}})]^{3+}$

C	-0.258500	-2.227300	2.809800
H	-0.611100	-3.169600	3.251300
H	-0.292000	-1.485900	3.611200
C	1.176500	-2.425300	2.327200
H	1.786200	-2.772500	3.172600
H	1.216800	-3.214200	1.573000
C	2.227300	-0.259200	2.809600
H	3.169300	-0.611800	3.251500
H	1.485400	-0.292800	3.610700
C	2.425300	1.175900	2.327300
H	2.772600	1.785500	3.172800
H	3.214000	1.216300	1.572900
C	0.259400	2.226700	2.810300
H	0.612300	3.168700	3.252100
H	0.293300	1.484800	3.611300
C	-1.175700	2.424800	2.328400
H	-1.785100	2.771700	3.174200
H	-1.216400	3.213900	1.574500

C	-2.226200	0.258700	2.810600
H	-1.484100	0.292100	3.611400
H	-3.168100	0.611200	3.252800
C	-2.424400	-1.176200	2.328100
H	-2.771100	-1.786000	3.173700
H	-3.213600	-1.216500	1.574300
C	-1.582000	-2.947200	0.885500
H	-2.209400	-3.640500	1.461900
H	-0.674400	-3.496000	0.613500
C	-2.294300	-2.549300	-0.389500
C	-3.249400	-3.373400	-0.978400
H	-3.554400	-4.308500	-0.519200
C	-3.802300	-2.951600	-2.192000
H	-4.549100	-3.547900	-2.711000
C	2.947800	-1.582400	0.885300
H	3.640800	-2.210300	1.461600
H	3.496900	-0.674800	0.614000
C	2.549700	-2.294000	-0.390100
C	3.373800	-3.248500	-0.979700
H	4.309100	-3.553600	-0.521000
C	2.951800	-3.800800	-2.193600
H	3.548200	-4.547100	-2.713200
C	1.581700	2.947400	0.885400
H	2.208700	3.641100	1.461700
H	0.673600	3.495400	0.613600
C	2.293900	2.549700	-0.389600
C	3.248000	3.374400	-0.979200
H	3.552700	4.309700	-0.520500
C	3.800300	2.952700	-2.193200
H	4.546300	3.549600	-2.712900
C	-2.947300	1.582200	0.886500
H	-3.640100	2.209900	1.463000
H	-3.496300	0.674600	0.615000
C	-2.549600	2.294200	-0.388800
C	-3.374300	3.248200	-0.978500
H	-4.309500	3.553200	-0.519600
C	-2.952900	3.800100	-2.192900
H	-3.549900	4.545900	-2.712700
N	-1.193100	-1.783200	1.732700
N	1.783600	-1.193800	1.732300
N	1.193600	1.783000	1.732700
N	-1.782800	1.193400	1.733400
N	-1.936100	-1.381300	-0.971900
N	1.381500	-1.935800	-0.972000
N	1.936300	1.381300	-0.971700

N	-1.381600	1.936400	-0.971200
C	2.538900	1.068000	-2.138400
C	-1.068300	2.538600	-2.138200
C	-2.539300	-1.067600	-2.138400
C	1.067600	-2.538500	-2.138600
H	2.251700	0.128200	-2.601700
H	-0.128600	2.251100	-2.601600
H	0.127800	-2.250900	-2.601700
H	-2.251600	-0.128200	-2.602100
N	3.445000	1.797300	-2.771000
N	1.796300	-3.445000	-2.771200
N	-3.446500	-1.796400	-2.770300
N	-1.797700	3.444400	-2.771000
Bi	0.000300	0.000000	0.206000

Zero-point correction=	0.650606 (Hartree/Particle)
Thermal correction to Energy=	0.685036
Thermal correction to Enthalpy=	0.685981
Thermal correction to Gibbs Free Energy=	0.586441
Sum of electronic and zero-point Energies=	-1749.540789
Sum of electronic and thermal Energies=	-1749.506359
Sum of electronic and thermal Enthalpies=	-1749.505415
Sum of electronic and thermal Free Energies=	-1749.604954

E(SCF) in SMD Solvation Model= -1750.69765961

Table S7. DFT-optimized Cartesian coordinates and energies for $[\text{Bi}(\text{L}^{\text{pz}})]^{3+}$

C	2.217900	-0.311600	2.797900
H	3.151100	-0.690200	3.236700
H	1.475500	-0.328100	3.598700
C	2.448700	1.118900	2.318900
H	2.802200	1.721400	3.166200
H	3.240600	1.145500	1.568000
C	0.305600	2.216000	2.799300
H	0.683200	3.148900	3.239400
H	0.319800	1.473200	3.599700
C	-1.123600	2.447300	2.316500
H	-1.728300	2.801600	3.162000
H	-1.147700	3.238800	1.565100
C	-2.221000	0.304500	2.795700
H	-3.154600	0.682300	3.234200
H	-1.479300	0.319100	3.597200
C	-2.451300	-1.125000	2.313500
H	-2.805600	-1.729300	3.159300

H	-3.242700	-1.150100	1.562000
C	-0.308600	-2.222600	2.794200
H	-0.323700	-1.481200	3.595900
H	-0.687000	-3.156300	3.232200
C	1.121000	-2.453400	2.312800
H	1.724500	-2.809400	3.158400
H	1.146000	-3.243600	1.559900
C	2.904200	-1.641100	0.861700
H	3.591500	-2.274000	1.439300
H	3.463300	-0.741400	0.585300
C	2.483300	-2.360400	-0.399800
C	3.282100	-3.363900	-0.966800
H	4.199000	-3.690200	-0.479600
C	1.835900	-3.577200	-2.714300
H	1.575300	-4.063400	-3.651100
C	1.012200	-2.594100	-2.158400
H	0.085100	-2.298400	-2.639000
C	1.639800	2.902300	0.866400
H	2.271400	3.589500	1.445200
H	0.740700	3.461500	0.588100
C	2.361600	2.481600	-0.393700
C	3.367700	3.279400	-0.957300
H	3.694300	4.195200	-0.468100
C	3.582600	1.835700	-2.706000
H	4.070600	1.575600	-3.642100
C	2.596800	1.012800	-2.153700
H	2.300600	0.087200	-2.636800
C	-2.903900	1.637300	0.859800
H	-3.594200	2.266900	1.437400
H	-3.460300	0.737500	0.578300
C	-2.480700	2.361600	-0.397900
C	-3.275400	3.371300	-0.959300
H	-4.190700	3.699100	-0.470200
C	-1.829300	3.587000	-2.706700
H	-1.567000	4.076500	-3.641300
C	-1.009500	2.597500	-2.156000
H	-0.084200	2.300100	-2.638900
C	-1.639600	-2.904900	0.856800
H	-2.269100	-3.596000	1.433600
H	-0.739100	-3.460300	0.575200
C	-2.363100	-2.480800	-0.401200
C	-3.376100	-3.271800	-0.961900
H	-3.707600	-4.185500	-0.472100
C	-3.585800	-1.826100	-2.710400
H	-4.074100	-1.562700	-3.645400

C	-2.593400	-1.009700	-2.160300
H	-2.292200	-0.086000	-2.644000
N	1.750400	-1.232400	1.717000
N	1.228900	1.748500	1.720800
N	-1.751900	1.227400	1.717400
N	-1.230800	-1.753000	1.715300
N	1.338200	-1.984400	-1.003300
N	1.985000	1.337900	-0.999700
N	-1.337600	1.983600	-1.004000
N	-1.981000	-1.339600	-1.008000
N	-3.977400	-2.951400	-2.108000
N	2.965600	-3.962000	-2.115500
N	3.968100	2.963500	-2.104900
N	-2.956600	3.973800	-2.105200
Bi	0.000200	-0.001400	0.214700

Zero-point correction=	0.649935 (Hartree/Particle)
Thermal correction to Energy=	0.684258
Thermal correction to Enthalpy=	0.685202
Thermal correction to Gibbs Free Energy=	0.585960
Sum of electronic and zero-point Energies=	-1749.497588
Sum of electronic and thermal Energies=	-1749.463266
Sum of electronic and thermal Enthalpies=	-1749.462322
Sum of electronic and thermal Free Energies=	-1749.561563

E(SCF) in SMD Solvation Model= -1750.66255432

Table S8. DFT-optimized Cartesian coordinates and energies for [Bi(DOTA)]¹⁻

Bi	0.000000	0.000000	0.597000
N	1.074600	1.847700	-1.166800
C	0.000000	2.682900	-1.733200
H	0.375800	3.290800	-2.576000
H	-0.312900	3.388200	-0.961400
C	-1.215800	1.884500	-2.217000
H	-1.940300	2.592600	-2.660200
H	-0.912000	1.212400	-3.027500
N	-1.847600	1.074500	-1.166800
C	-2.682900	-0.000000	-1.733100
H	-3.290900	0.375800	-2.575900
H	-3.388100	-0.312800	-0.961300
C	1.884600	1.215900	-2.216900
H	2.592900	1.940400	-2.660000
H	1.212700	0.912100	-3.027500
C	1.880400	2.627500	-0.203100

H	2.297800	3.534200	-0.666900
H	2.705500	2.003700	0.151000
C	1.064200	3.036600	1.054200
O	0.140100	2.201700	1.417900
O	1.351100	4.098900	1.596500
C	-2.627400	1.880500	-0.203100
H	-3.534100	2.297800	-0.667000
H	-2.003500	2.705500	0.150900
C	-3.036600	1.064300	1.054200
O	-2.201700	0.140100	1.417800
O	-4.098800	1.351400	1.596600
N	-1.074600	-1.847700	-1.166800
C	0.000000	-2.682900	-1.733200
H	-0.375800	-3.290800	-2.576000
H	0.312900	-3.388200	-0.961400
C	1.215800	-1.884500	-2.217000
H	1.940300	-2.592600	-2.660200
H	0.912000	-1.212400	-3.027500
N	1.847600	-1.074500	-1.166800
C	2.682900	0.000000	-1.733100
C	2.627400	-1.880500	-0.203100
H	3.534100	-2.297800	-0.667000
H	2.003500	-2.705500	0.150900
C	3.036600	-1.064300	1.054200
O	2.201700	-0.140100	1.417800
O	-0.140100	-2.201700	1.417900
C	-1.064200	-3.036600	1.054200
C	-1.880400	-2.627500	-0.203100
C	-1.884600	-1.215900	-2.216900
H	-2.592900	-1.940400	-2.660000
H	-1.212700	-0.912100	-3.027500
H	-2.297800	-3.534200	-0.666900
H	-2.705500	-2.003700	0.151000
O	-1.351100	-4.098900	1.596500
O	4.098800	-1.351400	1.596600
H	3.290900	-0.375800	-2.575900
H	3.388100	0.312800	-0.961300

Zero-point correction=	0.425662 (Hartree/Particle)
Thermal correction to Energy=	0.452694
Thermal correction to Enthalpy=	0.453639
Thermal correction to Gibbs Free Energy=	0.370871
Sum of electronic and zero-point Energies=	-1450.065310
Sum of electronic and thermal Energies=	-1450.038277
Sum of electronic and thermal Enthalpies=	-1450.037333

Sum of electronic and thermal Free Energies= -1450.120101

E(SCF) in SMD Solvation Model= -1450.62301758

Table S9. DFT-optimized Cartesian coordinates and energies for [Bi(CHX-DTPA)]²⁻

Bi	0.723900	-0.626700	0.319400
O	3.036900	-1.249500	0.219900
O	5.212000	-0.645900	0.254400
O	0.309700	-0.168300	-2.045400
O	0.834800	0.885000	-3.969900
O	1.366100	1.074100	1.990900
O	0.769400	2.915200	3.159600
O	0.199500	-2.792200	-0.560000
O	-1.040800	-3.952600	-2.047600
O	-0.508300	-1.057700	2.392400
O	-2.348900	-1.791800	3.482800
N	2.321700	1.249300	-0.757900
N	-0.633800	1.660000	0.093900
N	-1.917400	-1.104900	-0.027000
C	1.699600	2.560200	-0.535600
C	0.170400	2.600200	-0.730400
C	-1.946700	1.388700	-0.581900
C	-2.707200	0.156800	-0.013400
C	-4.075300	-0.005200	-0.723800
C	-4.950100	1.251000	-0.667900
C	-4.199900	2.431600	-1.290500
C	-2.862600	2.639700	-0.571400
C	3.603100	1.086400	-0.051500
C	4.006000	-0.401300	0.145200
C	2.434600	0.906900	-2.181100
C	1.079000	0.522500	-2.812700
C	-0.740400	2.130600	1.493700
C	0.590800	2.042800	2.299000
C	-1.927400	-1.878600	-1.287000
C	-0.831300	-2.985200	-1.308500
C	-2.312500	-1.968100	1.106100
C	-1.688100	-1.559500	2.461600
H	2.114900	3.311800	-1.235200
H	1.952500	2.888600	0.471300
H	-0.135200	3.640100	-0.519500
H	-0.060300	2.408500	-1.779600
H	-1.681400	1.147900	-1.616400
H	-2.916100	0.357000	1.045000
H	-3.902400	-0.259200	-1.777100

H	-4.601900	-0.857900	-0.278900
H	-5.901800	1.071800	-1.189100
H	-5.202200	1.488800	0.376700
H	-4.801000	3.351200	-1.240200
H	-4.022700	2.227900	-2.357100
H	-3.071500	2.923800	0.468700
H	-2.326400	3.483400	-1.021700
H	3.482500	1.506900	0.951000
H	4.427300	1.609400	-0.561900
H	3.089200	0.032000	-2.260200
H	2.888900	1.726200	-2.762400
H	-1.455900	1.495900	2.023600
H	-1.091300	3.171000	1.545700
H	-1.707100	-1.209100	-2.121400
H	-2.893100	-2.373200	-1.463200
H	-3.405900	-2.025900	1.216500
H	-1.953600	-2.978600	0.892400

Zero-point correction=	0.439000 (Hartree/Particle)
Thermal correction to Energy=	0.469132
Thermal correction to Enthalpy=	0.470077
Thermal correction to Gibbs Free Energy=	0.378847
Sum of electronic and zero-point Energies=	-1621.989005
Sum of electronic and thermal Energies=	-1621.958873
Sum of electronic and thermal Enthalpies=	-1621.957928
Sum of electronic and thermal Free Energies=	-1622.049158

E(SCF) in SMD Solvation Model= -1622.70250741

Table S10. DFT-optimized Cartesian coordinates and energies for $[\text{La}(\text{L}^{\text{py}})(\text{OH}_2)]^{3+}$

O	-0.000100	0.000100	-2.672500
H	-0.423900	-0.650000	-3.257300
H	0.423700	0.650200	-3.257300
N	-0.256200	-2.131500	1.760000
N	0.256300	2.131400	1.760100
N	-2.136100	0.255100	1.778300
N	2.300600	-1.234100	-0.875300
N	-2.300700	1.234100	-0.875100
N	2.136100	-0.255200	1.778200
N	-1.281800	-2.248500	-0.885200
N	1.281700	2.248500	-0.885100
C	2.079100	0.774400	2.858800
H	3.065500	0.882400	3.333300
H	1.411300	0.407000	3.640900

C	-2.079000	-0.774500	2.858900
H	-3.065300	-0.882600	3.333500
H	-1.411100	-0.407100	3.640900
C	1.620900	2.147000	2.374500
H	1.647700	2.847000	3.222100
H	2.322100	2.535500	1.633600
C	-3.457500	0.981300	-0.217800
C	-1.620800	-2.147100	2.374500
H	-2.322000	-2.535600	1.633600
H	-1.647500	-2.847200	3.222100
C	-0.772300	2.095100	2.844400
H	-0.878800	3.091100	3.298500
H	-0.399200	1.444600	3.637900
C	0.772400	-2.095200	2.844300
H	0.879000	-3.091300	3.298400
H	0.399400	-1.444700	3.637800
C	3.384900	-0.068300	0.986900
H	4.267600	-0.227600	1.622600
H	3.424600	0.973500	0.650800
C	3.531100	-2.606100	-2.436600
H	3.512000	-3.248500	-3.310600
C	-2.670400	-3.459700	-2.448100
H	-3.339300	-3.429100	-3.301700
C	3.457500	-0.981300	-0.218000
C	-0.993800	-3.416000	-0.262400
C	0.993800	3.416000	-0.262300
C	-3.531200	2.606200	-2.436300
H	-3.512200	3.248600	-3.310300
C	2.670200	3.459800	-2.448000
H	3.339100	3.429300	-3.301700
C	-3.384900	0.068300	0.987100
H	-4.267500	0.227500	1.622900
H	-3.424500	-0.973500	0.650900
C	-0.070200	-3.361500	0.938300
H	-0.220500	-4.259800	1.553900
H	0.969600	-3.388100	0.593900
C	0.070200	3.361500	0.938400
H	0.220500	4.259700	1.554100
H	-0.969600	3.388000	0.594100
C	-2.146600	1.623800	2.382200
H	-2.834500	1.656400	3.239800
H	-2.549600	2.315900	1.640200
C	-4.722000	2.331500	-1.761800
H	-5.663100	2.754800	-2.099600
C	-1.511300	-4.636100	-0.703400

H	-1.265400	-5.552400	-0.175400
C	2.146800	-1.624000	2.382000
H	2.834700	-1.656600	3.239600
H	2.549700	-2.316000	1.640000
C	4.679400	-1.512800	-0.633200
H	5.584900	-1.292500	-0.076300
C	-4.679400	1.512800	-0.632900
H	-5.584900	1.292500	-0.075900
C	4.721900	-2.331400	-1.762200
H	5.663000	-2.754700	-2.100100
C	1.511300	4.636200	-0.703200
H	1.265400	5.552400	-0.175200
C	2.120800	2.285900	-1.945900
H	2.375800	1.326100	-2.388800
C	-2.120900	-2.285800	-1.945800
H	-2.375900	-1.326000	-2.388800
C	2.354500	-2.039900	-1.958900
H	1.410700	-2.233400	-2.457700
C	-2.350200	-4.664100	-1.817300
H	-2.760100	-5.604200	-2.174000
C	2.350100	4.664200	-1.817200
H	2.760000	5.604300	-2.173900
C	-2.354600	2.040000	-1.958700
H	-1.410900	2.233500	-2.457600
La	0.000000	0.000000	0.007600

Zero-point correction= 0.722039 (Hartree/Particle)
 Thermal correction to Energy= 0.760165
 Thermal correction to Enthalpy= 0.761109
 Thermal correction to Gibbs Free Energy= 0.654357
 Sum of electronic and zero-point Energies= -2192.244322
 Sum of electronic and thermal Energies= -2192.206196
 Sum of electronic and thermal Enthalpies= -2192.205252
 Sum of electronic and thermal Free Energies= -2192.312003

E(SCF) in SMD Solvation Model= -2193.43670489

Table S11. DFT-optimized Cartesian coordinates and energies for $[\text{La}(\text{L}^{\text{pyd}})(\text{OH}_2)]^{3+}$

O	-0.078100	-0.219400	-2.492700
H	0.401100	-1.051300	-2.735600
H	-1.008200	-0.332600	-2.801200
La	-0.010300	0.008400	-0.016200
N	1.526600	-1.385200	1.916000
N	-1.775900	1.449800	1.687500

N	-1.563800	-1.626500	1.764800
N	2.258400	1.215200	-0.678100
N	-2.206000	-1.455200	-0.956400
N	1.280200	1.692700	1.855200
N	1.530000	-2.115100	-0.813900
N	-1.203800	2.241100	-0.890300
C	0.328300	2.229900	2.871600
H	0.751400	3.120200	3.359900
H	0.221000	1.483400	3.661100
C	-0.709100	-2.104600	2.891100
H	-1.178100	-2.966700	3.388200
H	-0.667800	-1.316400	3.644600
C	-1.042000	2.597700	2.307800
H	-1.643500	3.038000	3.116900
H	-0.933200	3.374500	1.548100
C	-2.765900	-2.457000	-0.271300
C	0.703700	-2.504900	2.470200
H	0.659200	-3.287300	1.706800
H	1.209300	-2.950100	3.340500
C	-2.344800	0.580200	2.756400
H	-3.242100	1.044300	3.192600
H	-1.616400	0.524500	3.567400
C	1.949200	-0.462900	3.014500
H	2.783800	-0.902700	3.580000
H	1.124000	-0.378700	3.723300
C	1.891100	2.823500	1.102400
H	2.556600	3.408800	1.754800
H	1.092400	3.502600	0.785000
C	2.648800	2.372200	-0.128900
C	2.500700	-2.628400	-0.051800
C	-2.362700	2.695800	-0.393300
C	-2.118000	-2.807700	1.050200
H	-2.838000	-3.341800	1.687800
H	-1.302000	-3.511400	0.849700
C	2.743300	-1.969600	1.289300
H	3.221200	-2.685700	1.973900
H	3.469600	-1.165500	1.127300
C	-2.877900	1.990400	0.843900
H	-3.512600	2.676600	1.424600
H	-3.522000	1.159900	0.533800
C	-2.713400	-0.824900	2.289100
H	-3.191400	-1.353100	3.127900
H	-3.463100	-0.767200	1.495800
C	-4.339800	-2.821500	-2.029000
H	-5.182200	-3.330200	-2.487000

C	3.319100	-3.675700	-0.513700
H	4.095100	-4.093000	0.121200
C	2.369900	0.924900	2.534600
H	2.748100	1.489800	3.399600
H	3.203600	0.840300	1.833800
C	3.687300	3.132200	-0.690000
H	4.005100	4.064400	-0.232300
C	-3.859000	-3.179300	-0.783400
H	-4.303600	-3.989500	-0.213100
C	4.282800	2.646500	-1.839600
H	5.088800	3.179300	-2.334400
C	-3.050500	3.758400	-0.999300
H	-3.986700	4.122900	-0.586900
C	3.105800	-4.143500	-1.796200
H	3.697600	-4.949000	-2.219400
C	-2.485900	4.321000	-2.130200
H	-2.959400	5.144400	-2.656000
C	-1.256500	3.802400	-2.571800
H	-0.746200	4.208800	-3.440000
C	-3.689700	-1.769500	-2.696800
H	-3.997900	-1.440800	-3.684900
C	3.819400	1.420100	-2.346200
H	4.250300	0.974800	-3.237900
C	2.091600	-3.528300	-2.549600
H	1.878800	-3.822500	-3.572900
N	2.840600	0.723100	-1.777200
N	-0.633700	2.794400	-1.966800
N	-2.657100	-1.117300	-2.171700
N	1.332500	-2.552600	-2.063500

Zero-point correction=	0.673191 (Hartree/Particle)
Thermal correction to Energy=	0.709931
Thermal correction to Enthalpy=	0.710875
Thermal correction to Gibbs Free Energy=	0.606795
Sum of electronic and zero-point Energies=	-2256.333403
Sum of electronic and thermal Energies=	-2256.296664
Sum of electronic and thermal Enthalpies=	-2256.295719
Sum of electronic and thermal Free Energies=	-2256.399799

E(SCF) in SMD Solvation Model= -2257.47747876

Table S12. DFT-optimized Cartesian coordinates and energies for $[\text{La}(\text{L}^{\text{pyr}})(\text{OH}_2)]^{3+}$

O	-0.000100	0.000100	-2.685900
H	-0.504300	-0.584100	-3.278200

H	0.504200	0.584300	-3.278200
N	-0.529600	-2.091500	1.763500
N	0.529700	2.091400	1.763600
N	-2.095400	0.529100	1.778100
N	2.131600	-1.495900	-0.866300
N	-2.131600	1.495900	-0.866100
N	2.095400	-0.529200	1.777900
N	-1.539000	-2.086600	-0.870200
N	1.539000	2.086700	-0.870200
C	2.163500	0.499700	2.860800
H	3.152200	0.481700	3.341800
H	1.450200	0.219900	3.638500
C	-2.163400	-0.499900	2.860900
H	-3.152100	-0.481900	3.341900
H	-1.450000	-0.220100	3.638600
C	1.886600	1.920700	2.378500
H	2.004200	2.608700	3.228000
H	2.633600	2.218000	1.639600
C	-3.320100	1.394300	-0.220800
C	-1.886500	-1.920900	2.378400
H	-2.633600	-2.218100	1.639500
H	-2.004100	-2.608800	3.227900
C	-0.497600	2.176300	2.848400
H	-0.477300	3.172800	3.312800
H	-0.212800	1.475900	3.635700
C	0.497700	-2.176500	2.848200
H	0.477400	-3.173000	3.312600
H	0.213000	-1.476100	3.635600
C	3.371200	-0.515100	1.008300
H	4.211100	-0.822300	1.647600
H	3.579300	0.513800	0.694600
C	3.320100	-1.394300	-0.221000
C	-1.408800	-3.286800	-0.251000
C	1.408800	3.286800	-0.250900
C	-3.371200	0.515100	1.008400
H	-4.211000	0.822200	1.647900
H	-3.579300	-0.513900	0.694700
C	-0.515100	-3.352500	0.968900
H	-0.810600	-4.207300	1.593800
H	0.512500	-3.546600	0.641500
C	0.515200	3.352400	0.969100
H	0.810700	4.207200	1.594000
H	-0.512500	3.546600	0.641700
C	-1.920800	1.889500	2.381900
H	-2.599800	2.012700	3.238000

H	-2.228700	2.629300	1.639900
C	-4.309100	2.826700	-1.850600
H	-5.150100	3.368600	-2.276900
C	-2.066000	-4.414400	-0.737200
H	-1.974300	-5.378500	-0.247200
C	1.920900	-1.889700	2.381700
H	2.600000	-2.012900	3.237800
H	2.228800	-2.629400	1.639600
C	4.450100	-2.056500	-0.693200
H	5.404500	-1.984400	-0.181700
C	-4.450100	2.056600	-0.692900
H	-5.404500	1.984500	-0.181300
C	4.309000	-2.826600	-1.851000
H	5.150000	-3.368500	-2.277300
C	2.066000	4.414500	-0.737100
H	1.974300	5.378500	-0.247000
C	2.358300	2.051400	-1.944200
H	2.508400	1.078600	-2.409100
C	-2.358400	-2.051300	-1.944200
H	-2.508500	-1.078400	-2.409100
C	2.111900	-2.281500	-1.965500
H	1.158900	-2.376400	-2.476800
C	-2.854600	-4.260900	-1.881000
H	-3.384400	-5.102100	-2.321800
C	2.854500	4.261000	-1.880900
H	3.384300	5.102200	-2.321700
C	-2.112000	2.281600	-1.965300
H	-1.159000	2.376500	-2.476600
N	3.010800	3.070500	-2.478400
N	-3.132800	2.946100	-2.482600
N	-3.010900	-3.070400	-2.478500
N	3.132700	-2.946000	-2.482900
La	-0.000000	-0.000000	0.012500

Zero-point correction=	0.674225 (Hartree/Particle)
Thermal correction to Energy=	0.711897
Thermal correction to Enthalpy=	0.712841
Thermal correction to Gibbs Free Energy=	0.606789
Sum of electronic and zero-point Energies=	-2256.397615
Sum of electronic and thermal Energies=	-2256.359943
Sum of electronic and thermal Enthalpies=	-2256.358998
Sum of electronic and thermal Free Energies=	-2256.465051

E(SCF) in SMD Solvation Model= -2257.59923093

Table S13. DFT-optimized Cartesian coordinates and energies for $[\text{La}(\text{L}^{\text{pz}})(\text{OH}_2)]^{3+}$

O	-0.000100	0.000100	-2.666000
H	-0.478100	-0.609000	-3.254200
H	0.478000	0.609200	-3.254100
N	-0.463900	-2.101400	1.748700
N	0.464000	2.101300	1.748800
N	-2.106600	0.463400	1.766600
N	2.191700	-1.440700	-0.897600
N	-2.191800	1.440800	-0.897400
N	2.106700	-0.463500	1.766400
N	-1.490900	-2.135700	-0.904300
N	1.490800	2.135700	-0.904200
C	2.146500	0.567500	2.849900
H	3.137100	0.579000	3.326700
H	1.444800	0.265400	3.630000
C	-2.146300	-0.567600	2.849900
H	-3.136900	-0.579200	3.326900
H	-1.444600	-0.265600	3.630000
C	1.825100	1.978700	2.366900
H	1.916800	2.670800	3.216000
H	2.563500	2.301000	1.630000
C	-3.356400	1.299200	-0.227900
C	-1.825000	-1.978800	2.366900
H	-2.563500	-2.301100	1.630000
H	-1.916600	-2.671000	3.215900
C	-0.565100	2.162000	2.834900
H	-0.573800	3.162000	3.291700
H	-0.257000	1.476200	3.626400
C	0.565200	-2.162200	2.834800
H	0.574000	-3.162200	3.291500
H	0.257200	-1.476300	3.626300
C	3.378500	-0.404800	0.989100
H	4.231500	-0.674400	1.628100
H	3.543900	0.631000	0.672700
C	3.356400	-1.299200	-0.228100
C	-1.315800	-3.313500	-0.267200
C	1.315800	3.313500	-0.267100
C	-3.378500	0.404800	0.989300
H	-4.231400	0.674300	1.628400
H	-3.543900	-0.631000	0.672900
C	-0.405400	-3.354400	0.940200
H	-0.662100	-4.225100	1.560400
H	0.628500	-3.503800	0.609100
C	0.405400	3.354300	0.940400

H	0.662100	4.225000	1.560600
H	-0.628500	3.503800	0.609300
C	-1.978900	1.828700	2.372200
H	-2.659700	1.926600	3.230000
H	-2.314600	2.558400	1.632500
C	-1.964800	-4.470000	-0.727500
H	-1.835000	-5.421900	-0.216200
C	1.979000	-1.828800	2.372000
H	2.659800	-1.926700	3.229700
H	2.314700	-2.558500	1.632300
C	4.514800	-1.954100	-0.670700
H	5.454400	-1.849200	-0.131800
C	-4.514800	1.954100	-0.670300
H	-5.454400	1.849200	-0.131400
C	1.964800	4.470100	-0.727400
H	1.834900	5.421900	-0.216000
C	2.951100	3.295300	-2.410700
H	3.618400	3.283100	-3.269000
C	-3.372500	2.876400	-2.409800
H	-3.373500	3.517500	-3.287700
C	3.372400	-2.876200	-2.410100
H	3.373400	-3.517300	-3.288100
C	-2.951200	-3.295100	-2.410800
H	-3.618500	-3.283000	-3.269000
C	-2.206700	2.236700	-1.985100
H	-1.273600	2.363000	-2.523200
C	2.323000	2.131000	-1.966500
H	2.507600	1.176100	-2.452200
C	2.206600	-2.236600	-1.985300
H	1.273400	-2.362900	-2.523400
C	-2.323100	-2.130900	-1.966500
H	-2.507700	-1.176000	-2.452100
N	4.526900	-2.730300	-1.754600
N	2.764000	4.465700	-1.793600
N	-4.527000	2.730400	-1.754200
N	-2.764100	-4.465600	-1.793800
La	-0.000000	-0.000000	0.016100

Zero-point correction=	0.673175 (Hartree/Particle)
Thermal correction to Energy=	0.710849
Thermal correction to Enthalpy=	0.711793
Thermal correction to Gibbs Free Energy=	0.605684
Sum of electronic and zero-point Energies=	-2256.351134
Sum of electronic and thermal Energies=	-2256.313459
Sum of electronic and thermal Enthalpies=	-2256.312515

Sum of electronic and thermal Free Energies= -2256.418624

E(SCF) in SMD Solvation Model= -2257.56672330

Table S14. DFT-optimized Cartesian coordinates and energies for [La(DOTA)(OH₂)]¹⁻

N	0.847000	1.906200	1.305600
N	-1.135900	-1.908300	1.156900
N	1.757500	-0.990600	1.407400
N	-2.046900	0.994800	1.071200
O	1.946400	1.467700	-1.176700
O	1.614800	-1.838500	-1.198600
O	-1.719400	-1.505500	-1.488100
O	-1.387800	1.832600	-1.442400
O	-3.398600	2.850300	-1.669400
O	2.899100	3.519900	-1.161000
O	-2.741100	-3.523400	-1.605100
O	3.705100	-2.699400	-1.102500
C	2.778700	-2.027200	-0.660000
C	3.007300	-1.253800	0.662600
C	1.970700	-0.014700	2.488400
C	1.227300	-2.265000	1.931300
C	-0.258000	-2.222300	2.295800
C	2.062300	1.431800	1.997500
C	2.118900	2.675700	-0.734800
C	1.187800	3.061400	0.444400
C	-0.210700	2.237200	2.276000
C	-1.617200	2.272600	1.675800
C	-3.128000	1.255600	0.093500
C	-2.453500	0.026200	2.101800
C	-2.620000	2.077000	-1.122800
C	-2.454300	-1.425500	1.616800
C	-1.324200	-3.078000	0.268800
C	-2.015400	-2.694500	-1.066900
H	3.738000	-1.799700	1.281100
H	3.455600	-0.295900	0.381300
H	2.891200	-0.248500	3.055600
H	1.145900	-0.106500	3.202200
H	1.797900	-2.592200	2.820500
H	1.387500	-3.023900	1.163100
H	-0.531900	-3.193600	2.748200
H	-0.423700	-1.470100	3.074000
H	2.301600	2.080300	2.860700
H	2.897900	1.525900	1.301800
H	1.656500	3.872500	1.024300

H	0.265700	3.448100	-0.001500
H	-0.013300	3.214800	2.754400
H	-0.178400	1.496300	3.081300
H	-2.324300	2.591900	2.463800
H	-1.659000	3.037000	0.898000
H	-3.977100	1.779900	0.560500
H	-3.489200	0.298200	-0.295800
H	-3.462200	0.262000	2.489600
H	-1.772200	0.127200	2.953300
H	-2.844800	-2.065700	2.429300
H	-3.151300	-1.527300	0.782900
H	-1.902800	-3.872800	0.766200
H	-0.340700	-3.483600	0.010100
La	-0.006900	-0.003000	-0.765000
H	1.722400	0.598900	-2.916200
H	1.523200	-0.934500	-2.961200
O	1.094100	-0.091500	-3.220600

Zero-point correction=	0.451448 (Hartree/Particle)
Thermal correction to Energy=	0.480878
Thermal correction to Enthalpy=	0.481823
Thermal correction to Gibbs Free Energy=	0.393508
Sum of electronic and zero-point Energies=	-1956.951495
Sum of electronic and thermal Energies=	-1956.922064
Sum of electronic and thermal Enthalpies=	-1956.921120
Sum of electronic and thermal Free Energies=	-1957.009434

E(SCF) in SMD Solvation Model= -1957.55114800

Table S15. DFT-optimized Cartesian coordinates and energies for [La(CHX-DTPA)(OH₂)]²⁻

La	-0.901700	0.808300	0.144400
O	-3.275400	1.015700	-0.269800
O	-5.429200	0.322800	-0.320500
O	-0.483300	-0.348100	-2.014600
O	-0.654000	-2.079500	-3.455600
O	-1.332900	-0.424700	2.210200
O	-0.795400	-1.876900	3.858200
O	0.012000	2.632800	-1.285300
O	1.367600	3.335700	-2.950500
O	0.624000	1.845200	1.938400
O	2.584900	2.514100	2.851700
N	-2.388600	-1.573100	-0.392100
N	0.587900	-1.631200	0.549600
N	1.998600	0.961300	-0.337500

C	-1.738800	-2.706000	0.272400
C	-0.217000	-2.785600	0.072200
C	1.890100	-1.602100	-0.200200
C	2.720200	-0.301300	-0.010900
C	4.069400	-0.412800	-0.772400
C	4.902900	-1.635500	-0.381000
C	4.089800	-2.906000	-0.634300
C	2.766600	-2.841700	0.134800
C	-3.727400	-1.296800	0.150300
C	-4.216200	0.135900	-0.194300
C	-2.415600	-1.725500	-1.855400
C	-1.063100	-1.378500	-2.520700
C	0.719700	-1.659700	2.023500
C	-0.591700	-1.302800	2.783400
C	2.001100	1.357900	-1.763700
C	1.059100	2.562300	-2.041200
C	2.521900	2.055900	0.505600
C	1.881200	2.132100	1.910400
H	-2.145900	-3.667900	-0.103100
H	-1.975100	-2.658700	1.335400
H	0.105000	-3.711700	0.581600
H	-0.009100	-2.925200	-0.991300
H	1.602800	-1.647900	-1.256400
H	2.965000	-0.223400	1.056300
H	3.868300	-0.464900	-1.850000
H	4.641600	0.507800	-0.606900
H	5.844700	-1.649900	-0.949000
H	5.176500	-1.581100	0.683600
H	4.653700	-3.802700	-0.337900
H	3.890900	-3.000200	-1.712300
H	2.993200	-2.837200	1.209900
H	2.189400	-3.753300	-0.055300
H	-3.658700	-1.351000	1.242700
H	-4.479700	-2.029400	-0.187000
H	-3.155900	-1.020600	-2.250000
H	-2.726100	-2.741800	-2.153000
H	1.455200	-0.907600	2.326100
H	1.061100	-2.639100	2.392200
H	1.624100	0.522900	-2.362000
H	3.000000	1.642300	-2.125200
H	3.617100	2.018900	0.611300
H	2.285300	3.004700	0.013800
H	-0.556600	3.240400	1.544200
H	-0.827800	3.650000	0.084300
O	-1.286100	3.502200	0.939600

Zero-point correction=	0.464379 (Hartree/Particle)
Thermal correction to Energy=	0.496939
Thermal correction to Enthalpy=	0.497884
Thermal correction to Gibbs Free Energy=	0.401433
Sum of electronic and zero-point Energies=	-2128.875952
Sum of electronic and thermal Energies=	-2128.843392
Sum of electronic and thermal Enthalpies=	-2128.842448
Sum of electronic and thermal Free Energies=	-2128.938898

E(SCF) in SMD Solvation Model= -2129.63005426

Table S16. DFT-optimized Cartesian coordinates and energies for $[\text{Ac}(\text{L}^{\text{py}})(\text{OH}_2)]^{3+}$

O	0.000300	-0.000300	-2.848200
H	0.570000	0.523600	-3.437200
H	-0.569700	-0.524000	-3.437000
N	0.554100	2.097300	1.775100
N	-0.554200	-2.097100	1.775100
N	2.100900	-0.554100	1.789400
N	-2.221800	1.532200	-0.896700
N	2.221800	-1.532500	-0.896400
N	-2.101000	0.554200	1.789200
N	1.600000	2.163800	-0.886800
N	-1.600000	-2.163700	-0.886700
C	-2.164900	-0.476100	2.869300
H	-3.149100	-0.450800	3.360300
H	-1.442000	-0.203300	3.640700
C	2.164800	0.476300	2.869400
H	3.148900	0.450900	3.360500
H	1.441800	0.203500	3.640700
C	-1.905400	-1.903800	2.389500
H	-2.034000	-2.586000	3.242700
H	-2.655800	-2.193000	1.651000
C	3.370500	-1.453900	-0.183200
C	1.905300	1.903900	2.389500
H	2.655700	2.193100	1.651000
H	2.033900	2.586200	3.242700
C	0.476500	-2.182100	2.855000
H	0.450000	-3.176100	3.325700
H	0.200000	-1.475200	3.639600
C	-0.476700	2.182300	2.854900
H	-0.450200	3.176200	3.325600
H	-0.200100	1.475400	3.639500
C	-3.382700	0.542700	1.027600

H	-4.218600	0.822400	1.685000
H	-3.575900	-0.485000	0.699900
C	-3.308600	3.060800	-2.419000
H	-3.236700	3.688600	-3.300900
C	3.143200	3.234100	-2.406800
H	3.802100	3.146900	-3.264300
C	-3.370500	1.453800	-0.183400
C	1.474000	3.332600	-0.215000
C	-1.474000	-3.332500	-0.214900
C	3.308600	-3.061300	-2.418500
H	3.236700	-3.689100	-3.300300
C	-3.143200	-3.233900	-2.406800
H	-3.802100	-3.146600	-3.264300
C	3.382700	-0.542600	1.027800
H	4.218500	-0.822300	1.685300
H	3.576000	0.485000	0.700000
C	0.545800	3.362200	0.985300
H	0.813200	4.214500	1.626500
H	-0.479500	3.542500	0.642000
C	-0.545900	-3.362100	0.985400
H	-0.813300	-4.214400	1.626600
H	0.479400	-3.542500	0.642100
C	1.905100	-1.910700	2.388700
H	2.580700	-2.048000	3.246200
H	2.203100	-2.651200	1.643400
C	4.494300	-2.965200	-1.688200
H	5.379100	-3.518000	-1.989600
C	2.155700	4.486600	-0.608700
H	2.039400	5.406100	-0.043200
C	-1.905200	1.910800	2.388500
H	-2.580800	2.048200	3.245900
H	-2.203200	2.651300	1.643200
C	-4.519500	2.156300	-0.551300
H	-5.421500	2.075200	0.047400
C	4.519600	-2.156400	-0.551000
H	5.421500	-2.075200	0.047700
C	-4.494300	2.965000	-1.688600
H	-5.379100	3.517700	-1.990100
C	-2.155800	-4.486500	-0.608600
H	-2.039500	-5.406000	-0.043200
C	-2.436100	-2.128000	-1.948500
H	-2.559100	-1.159800	-2.429800
C	2.436100	2.128200	-1.948600
H	2.559100	1.160100	-2.429800
C	-2.205700	2.332600	-1.985700

H	-1.264900	2.385900	-2.525000
C	2.990900	4.443900	-1.725500
H	3.526300	5.332600	-2.045900
C	-2.991000	-4.443700	-1.725500
H	-3.526400	-5.332400	-2.046000
C	2.205600	-2.333000	-1.985300
H	1.264800	-2.386400	-2.524600
Ac	0.000000	0.000000	-0.071800

Zero-point correction=	0.720717 (Hartree/Particle)
Thermal correction to Energy=	0.759393
Thermal correction to Enthalpy=	0.760337
Thermal correction to Gibbs Free Energy=	0.651308
Sum of electronic and zero-point Energies=	-2132.305839
Sum of electronic and thermal Energies=	-2132.267162
Sum of electronic and thermal Enthalpies=	-2132.266218
Sum of electronic and thermal Free Energies=	-2132.375247

E(SCF) in SMD Solvation Model= -2133.52670781

Table S17. DFT-optimized Cartesian coordinates and energies for $[\text{Ac}(\text{L}^{\text{pyd}})(\text{OH}_2)]^{3+}$

O	-0.130400	-0.453500	-2.642900
H	0.386800	-1.272500	-2.841900
H	-1.058200	-0.616800	-2.928300
N	1.571600	-1.374000	1.922100
N	-1.758000	1.511700	1.726000
N	-1.555400	-1.598800	1.824000
N	2.290200	1.351400	-0.724200
N	-2.260800	-1.568300	-0.914800
N	1.343200	1.740700	1.848700
N	1.627400	-2.183700	-0.811800
N	-1.355300	2.247200	-0.917300
C	0.391000	2.267100	2.869800
H	0.814000	3.153000	3.366800
H	0.283800	1.515300	3.653800
C	-0.669800	-2.053100	2.936600
H	-1.127500	-2.902000	3.466000
H	-0.606600	-1.249300	3.671200
C	-0.981900	2.647200	2.315000
H	-1.559400	3.119200	3.124700
H	-0.867000	3.405800	1.536700
C	-2.825100	-2.508100	-0.149800
C	0.732800	-2.473300	2.493400
H	0.664300	-3.258800	1.734300

H	1.242000	-2.923600	3.359400
C	-2.289300	0.637700	2.810100
H	-3.170700	1.100300	3.279700
H	-1.535000	0.577400	3.596200
C	1.997200	-0.432600	3.003900
H	2.831100	-0.865800	3.575700
H	1.174600	-0.335300	3.713400
C	1.966800	2.885300	1.127800
H	2.645400	3.439300	1.794200
H	1.176600	3.588600	0.841700
C	2.710300	2.472200	-0.126600
C	2.573100	-2.678900	-0.006600
C	-2.455200	2.746400	-0.339300
C	-2.144500	-2.799700	1.171000
H	-2.853300	-3.296800	1.849900
H	-1.342500	-3.522300	0.981400
C	2.790800	-1.982400	1.321900
H	3.255400	-2.684200	2.030400
H	3.525200	-1.186800	1.153400
C	-2.895200	2.075100	0.946300
H	-3.470500	2.787500	1.557100
H	-3.583800	1.260600	0.694300
C	-2.680500	-0.767300	2.354500
H	-3.160300	-1.279400	3.202700
H	-3.436600	-0.703200	1.566900
C	-4.457500	-2.944300	-1.837000
H	-5.324800	-3.459600	-2.237700
C	3.393900	-3.748000	-0.411500
H	4.150100	-4.149700	0.256600
C	2.426100	0.949900	2.510500
H	2.830600	1.506800	3.369400
H	3.246400	0.850800	1.794900
C	3.761500	3.232300	-0.664800
H	4.105400	4.136700	-0.171400
C	-3.950400	-3.232500	-0.583700
H	-4.399100	-3.991800	0.050000
C	4.335800	2.783300	-1.840600
H	5.149300	3.319400	-2.319200
C	-3.159100	3.814200	-0.918500
H	-4.047700	4.219200	-0.443300
C	3.208300	-4.259300	-1.681800
H	3.804800	-5.082700	-2.061900
C	-2.673800	4.327700	-2.108800
H	-3.165500	5.151400	-2.617100
C	-1.503500	3.757700	-2.639900

H	-1.058800	4.119300	-3.562000
C	-3.801600	-1.955500	-2.590500
H	-4.129700	-1.684000	-3.589400
C	3.840800	1.591300	-2.398700
H	4.251800	1.176400	-3.313800
C	2.213400	-3.668900	-2.479800
H	2.018800	-4.002600	-3.494500
N	2.850300	0.893900	-1.849700
N	-0.862700	2.748300	-2.055800
N	-2.738200	-1.297200	-2.137800
N	1.450800	-2.669900	-2.048000
Ac	0.000400	0.010700	-0.112600

Zero-point correction=	0.672283 (Hartree/Particle)
Thermal correction to Energy=	0.709433
Thermal correction to Enthalpy=	0.710377
Thermal correction to Gibbs Free Energy=	0.604673
Sum of electronic and zero-point Energies=	-2196.397044
Sum of electronic and thermal Energies=	-2196.359894
Sum of electronic and thermal Enthalpies=	-2196.358950
Sum of electronic and thermal Free Energies=	-2196.464653

E(SCF) in SMD Solvation Model= -2197.56971250

Table S18. DFT-optimized Cartesian coordinates and energies for $[\text{Ac}(\text{L}^{\text{pyr}})(\text{OH}_2)]^{3+}$

O	-0.000000	0.000200	-2.855300
H	-0.612200	-0.467900	-3.450400
H	0.612300	0.468200	-3.450300
N	-0.675400	-2.072900	1.784600
N	0.675500	2.072800	1.784700
N	-2.075700	0.676200	1.795300
N	2.154100	-1.616400	-0.891800
N	-2.154200	1.616500	-0.891700
N	2.075800	-0.676300	1.795200
N	-1.689400	-2.099400	-0.871000
N	1.689500	2.099400	-0.871000
C	2.187200	0.350400	2.877100
H	3.163000	0.269800	3.378100
H	1.442500	0.119200	3.640900
C	-2.187100	-0.350600	2.877200
H	-3.162800	-0.270000	3.378200
H	-1.442300	-0.119400	3.640900
C	2.014100	1.790700	2.395800
H	2.189500	2.464000	3.247600

H	2.778800	2.030800	1.653700
C	-3.309000	1.614200	-0.180100
C	-2.014100	-1.790800	2.395800
H	-2.778700	-2.030900	1.653700
H	-2.189400	-2.464100	3.247600
C	-0.351900	2.203400	2.865100
H	-0.270600	3.188200	3.347800
H	-0.118100	1.473200	3.641800
C	0.352100	-2.203600	2.865000
H	0.270700	-3.188400	3.347600
H	0.118200	-1.473400	3.641700
C	3.369800	-0.746800	1.059000
H	4.169900	-1.108800	1.720600
H	3.653000	0.268100	0.757500
C	3.309000	-1.614200	-0.180400
C	-1.634700	-3.277700	-0.201600
C	1.634700	3.277700	-0.201500
C	-3.369700	0.746800	1.059100
H	-4.169800	1.108700	1.720800
H	-3.653000	-0.268100	0.757600
C	-0.749400	-3.353800	1.025700
H	-1.099700	-4.168400	1.676000
H	0.263600	-3.627100	0.707600
C	0.749500	3.353700	1.025800
H	1.099800	4.168300	1.676200
H	-0.263500	3.627000	0.707800
C	-1.792500	2.020100	2.392000
H	-2.461900	2.204500	3.245200
H	-2.038300	2.775600	1.642000
C	-4.270400	3.102600	-1.778100
H	-5.089700	3.702800	-2.166800
C	-2.354200	-4.383500	-0.649000
H	-2.325400	-5.330600	-0.119600
C	1.792600	-2.020200	2.391800
H	2.462100	-2.204600	3.245000
H	2.038400	-2.775700	1.641700
C	4.407200	-2.359200	-0.601800
H	5.335500	-2.369200	-0.039600
C	-4.407200	2.359300	-0.601400
H	-5.335500	2.369300	-0.039200
C	4.270300	-3.102500	-1.778500
H	5.089600	-3.702600	-2.167300
C	2.354200	4.383600	-0.648800
H	2.325400	5.330600	-0.119500
C	2.495600	2.060000	-1.953700

H	2.587900	1.098800	-2.457200
C	-2.495600	-2.059900	-1.953700
H	-2.587900	-1.098700	-2.457200
C	2.132000	-2.386600	-2.001700
H	1.202000	-2.402000	-2.563000
C	-3.121800	-4.231000	-1.807600
H	-3.695700	-5.057400	-2.220100
C	3.121800	4.231100	-1.807500
H	3.695600	5.057600	-2.219900
C	-2.132200	2.386700	-2.001500
H	-1.202100	2.402000	-2.562800
N	3.202800	3.059200	-2.454900
N	-3.125400	3.123200	-2.474800
N	-3.202800	-3.059100	-2.455000
N	3.125300	-3.123100	-2.475100
Ac	-0.000000	0.000000	-0.069200

Zero-point correction=	0.672662 (Hartree/Particle)
Thermal correction to Energy=	0.711035
Thermal correction to Enthalpy=	0.711979
Thermal correction to Gibbs Free Energy=	0.602950
Sum of electronic and zero-point Energies=	-2196.459830
Sum of electronic and thermal Energies=	-2196.421457
Sum of electronic and thermal Enthalpies=	-2196.420512
Sum of electronic and thermal Free Energies=	-2196.529542

E(SCF) in SMD Solvation Model= -2197.69415301

Table S19. DFT-optimized Cartesian coordinates and energies for $[\text{Ac}(\text{L}^{\text{Pz}})(\text{OH}_2)]^{3+}$

O	0.000000	0.000200	-2.842800
H	-0.587000	-0.502000	-3.434700
H	0.586900	0.502500	-3.434600
N	-0.717700	-2.051100	1.763600
N	0.717800	2.051000	1.763700
N	-2.054900	0.718300	1.777500
N	2.136200	-1.678600	-0.930500
N	-2.136300	1.678600	-0.930400
N	2.054900	-0.718400	1.777400
N	-1.760100	-2.065100	-0.913100
N	1.760100	2.065100	-0.913000
C	2.190500	0.304300	2.861500
H	3.164600	0.199600	3.361000
H	1.440700	0.088800	3.625000
C	-2.190300	-0.304500	2.861600

H	-3.164400	-0.199800	3.361100
H	-1.440500	-0.089000	3.625000
C	2.049400	1.747900	2.380800
H	2.232000	2.418000	3.233300
H	2.822000	1.974500	1.643200
C	-3.266500	1.694700	-0.190000
C	-2.049300	-1.748000	2.380800
H	-2.822000	-1.974600	1.643200
H	-2.231800	-2.418200	3.233200
C	-0.305800	2.212500	2.845100
H	-0.200500	3.199000	3.319300
H	-0.086200	1.482800	3.626400
C	0.305900	-2.212700	2.844900
H	0.200700	-3.199200	3.319100
H	0.086400	-1.483000	3.626300
C	3.344100	-0.807800	1.031900
H	4.145000	-1.168300	1.693600
H	3.632500	0.203000	0.722000
C	3.266500	-1.694700	-0.190300
C	-1.723400	-3.222500	-0.217900
C	1.723500	3.222500	-0.217800
C	-3.344100	0.807700	1.032100
H	-4.144900	1.168200	1.693900
H	-3.632500	-0.203000	0.722200
C	-0.812700	-3.322100	0.987300
H	-1.158400	-4.142100	1.633500
H	0.195300	-3.597600	0.655400
C	0.812700	3.322100	0.987500
H	1.158500	4.142000	1.633700
H	-0.195200	3.597600	0.655600
C	-1.750200	2.057200	2.375400
H	-2.414800	2.251000	3.230000
H	-1.984900	2.817900	1.627500
C	-2.509600	-4.313400	-0.620600
H	-2.492900	-5.247800	-0.062900
C	1.750300	-2.057300	2.375200
H	2.415000	-2.251200	3.229800
H	1.985000	-2.818000	1.627200
C	4.351300	-2.498000	-0.570500
H	5.262100	-2.522400	0.024400
C	-4.351400	2.498000	-0.570100
H	-5.262200	2.522400	0.024900
C	2.509600	4.313500	-0.620400
H	2.493000	5.247800	-0.062700
C	3.358200	3.113300	-2.360700

H	4.023900	3.063400	-3.218700
C	-3.205400	3.253900	-2.386600
H	-3.175400	3.885400	-3.271000
C	3.205200	-3.253800	-2.387000
H	3.175100	-3.885200	-3.271400
C	-3.358100	-3.113200	-2.360800
H	-4.023900	-3.063300	-3.218800
C	-2.110600	2.466400	-2.023900
H	-1.201500	2.467400	-2.616800
C	2.591400	2.012900	-1.973700
H	2.665400	1.067700	-2.506500
C	2.110400	-2.466400	-2.024100
H	1.201200	-2.467300	-2.616900
C	-2.591400	-2.012800	-1.973800
H	-2.665500	-1.067600	-2.506600
N	4.325800	-3.265400	-1.660800
N	3.309000	4.265400	-1.685900
N	-4.326000	3.265500	-1.660400
N	-3.309000	-4.265300	-1.686000
Ac	-0.000000	0.000000	-0.071900

Zero-point correction= 0.671706 (Hartree/Particle)

Thermal correction to Energy= 0.710027

Thermal correction to Enthalpy= 0.710971

Thermal correction to Gibbs Free Energy= 0.602033

Sum of electronic and zero-point Energies= -2196.412949

Sum of electronic and thermal Energies= -2196.374628

Sum of electronic and thermal Enthalpies= -2196.373684

Sum of electronic and thermal Free Energies= -2196.482622

E(SCF) in SMD Solvation Model= -2197.65897545

Table S20. DFT-optimized Cartesian coordinates and energies for $[\text{Ac}(\text{DOTA})(\text{OH}_2)]^{1-}$

N	0.852400	1.907900	1.411200
N	-1.178100	-1.914700	1.235200
N	1.744300	-1.020300	1.510000
N	-2.067600	1.018700	1.151200
O	1.987400	1.567600	-1.095700
O	1.729600	-1.851900	-1.135300
O	-1.758900	-1.605300	-1.451700
O	-1.471400	1.888100	-1.397800
O	-3.494700	2.896500	-1.552200
O	2.942500	3.615600	-0.970900
O	-2.778500	-3.628500	-1.488100

O	3.789000	-2.762600	-0.906800
C	2.850400	-2.069700	-0.524000
C	3.019800	-1.304600	0.814900
C	1.940000	-0.040800	2.593500
C	1.183700	-2.286100	2.026100
C	-0.304500	-2.223100	2.380800
C	2.056000	1.405300	2.105000
C	2.157200	2.751400	-0.594600
C	1.215400	3.089200	0.593500
C	-0.215800	2.227100	2.376100
C	-1.616600	2.286300	1.762300
C	-3.164800	1.301600	0.196000
C	-2.475400	0.043600	2.177000
C	-2.691200	2.127200	-1.034400
C	-2.491400	-1.406100	1.684100
C	-1.386000	-3.107000	0.380000
C	-2.060500	-2.772500	-0.980500
H	3.710600	-1.866200	1.464100
H	3.500700	-0.353500	0.564300
H	2.845900	-0.281600	3.180300
H	1.099900	-0.124600	3.289200
H	1.740900	-2.624100	2.920000
H	1.340300	-3.047000	1.258300
H	-0.588900	-3.187300	2.841300
H	-0.466500	-1.463000	3.151600
H	2.305600	2.047100	2.970600
H	2.893600	1.486100	1.409500
H	1.686000	3.871700	1.209900
H	0.301300	3.506700	0.158400
H	-0.016300	3.194400	2.873700
H	-0.197800	1.472500	3.168400
H	-2.324600	2.618100	2.544500
H	-1.636700	3.050900	0.983600
H	-3.996000	1.831400	0.688100
H	-3.551100	0.351300	-0.188100
H	-3.481100	0.283900	2.569300
H	-1.791700	0.134200	3.027200
H	-2.902100	-2.043500	2.489100
H	-3.179500	-1.492400	0.840700
H	-1.984300	-3.871000	0.901800
H	-0.409900	-3.546900	0.149200
Ac	0.001700	-0.003700	-0.742800
H	1.867600	0.664300	-2.863800
H	1.732100	-0.881000	-2.915600
O	1.279700	-0.053700	-3.184500

Zero-point correction=	0.450361 (Hartree/Particle)
Thermal correction to Energy=	0.480247
Thermal correction to Enthalpy=	0.481191
Thermal correction to Gibbs Free Energy=	0.390962
Sum of electronic and zero-point Energies=	-1897.021615
Sum of electronic and thermal Energies=	-1896.991729
Sum of electronic and thermal Enthalpies=	-1896.990785
Sum of electronic and thermal Free Energies=	-1897.081014

E(SCF) in SMD Solvation Model= -1897.65258373

Table S21. DFT-optimized Cartesian coordinates and energies for [Ac(CHX-DTPA)(OH₂)]²⁻

Ac	0.841200	-0.763800	0.128900
O	3.326400	-0.881500	-0.271300
O	5.442100	-0.075500	-0.297000
O	0.422200	0.477900	-2.075200
O	0.625000	2.232000	-3.485800
O	1.216500	0.528800	2.271400
O	0.646800	2.013900	3.880300
O	-0.143100	-2.589900	-1.388100
O	-1.568500	-3.225500	-3.022400
O	-0.727400	-1.896200	1.917900
O	-2.711400	-2.521500	2.812500
N	2.313700	1.691300	-0.393900
N	-0.691400	1.717400	0.550200
N	-2.107000	-0.891500	-0.343900
C	1.634200	2.806100	0.276000
C	0.112500	2.870300	0.063600
C	-1.995000	1.677500	-0.200400
C	-2.822900	0.374600	-0.001800
C	-4.182500	0.487000	-0.745100
C	-5.010900	1.710000	-0.345800
C	-4.203200	2.977800	-0.625400
C	-2.870300	2.920500	0.126600
C	3.660800	1.457900	0.152900
C	4.218800	0.046600	-0.186500
C	2.351600	1.862600	-1.856000
C	1.011800	1.518100	-2.551400
C	-0.832500	1.766600	2.023600
C	0.466600	1.419800	2.811800
C	-2.125200	-1.263500	-1.779100
C	-1.213400	-2.480800	-2.105700
C	-2.642400	-1.996200	0.483000

C	-1.995200	-2.134900	1.882900
H	2.031500	3.777500	-0.084600
H	1.860600	2.749300	1.340700
H	-0.217400	3.799200	0.562400
H	-0.091300	2.998300	-1.001800
H	-1.707200	1.716000	-1.256800
H	-3.051700	0.292100	1.068400
H	-3.996500	0.540200	-1.825200
H	-4.752900	-0.433300	-0.572800
H	-5.962700	1.718000	-0.896800
H	-5.264800	1.663900	0.724100
H	-4.761700	3.878000	-0.329500
H	-4.020500	3.060600	-1.707100
H	-3.085100	2.930100	1.203800
H	-2.294400	3.828900	-0.081500
H	3.590600	1.510000	1.245700
H	4.384400	2.220100	-0.181000
H	3.101300	1.168600	-2.253300
H	2.659700	2.885000	-2.133900
H	-1.576200	1.023700	2.330800
H	-1.174700	2.752300	2.373100
H	-1.743000	-0.421600	-2.365300
H	-3.132200	-1.522400	-2.134800
H	-3.734200	-1.935600	0.603400
H	-2.437000	-2.937800	-0.036700
H	0.429700	-3.310900	1.440600
H	0.685200	-3.668100	-0.039200
O	1.147900	-3.568600	0.820900

Zero-point correction=	0.463724 (Hartree/Particle)
Thermal correction to Energy=	0.496543
Thermal correction to Enthalpy=	0.497487
Thermal correction to Gibbs Free Energy=	0.399984
Sum of electronic and zero-point Energies=	-2068.952630
Sum of electronic and thermal Energies=	-2068.919810
Sum of electronic and thermal Enthalpies=	-2068.918866
Sum of electronic and thermal Free Energies=	-2069.016370

E(SCF) in SMD Solvation Model= -2069.73354452

Figure 1

Figure 2

Figure 3

$$R_f = 1$$

Free metal ion

$$R_f = 0$$

Metal complex

Figure 4

Figure 5

(a)

(b)

(c)

Figure 6

Figure 7

(a)

(b)

(c)

(d)

Figure 8

Figure 9