

# Chelating the Alpha Therapy Radionuclides $^{225}\text{Ac}^{3+}$ and $^{213}\text{Bi}^{3+}$ with 18-Membered Macrocyclic Ligands MacroDipa and Py-MacroDipa

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**ABSTRACT:** The radionuclides  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$  possess favorable physical properties for targeted alpha therapy (TAT), a therapeutic approach that leverages  $\alpha$  radiation to treat cancers. A chelator that effectively binds and retains these radionuclides is required for this application. The development of ligands for this purpose, however, is challenging because the large ionic radii and charge-diffuse nature of these metal ions give rise to weaker metal–ligand interactions. In this study, we evaluated two 18-membered macrocyclic chelators, macroDipa and py-macroDipa, for their ability to complex  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$ . Their coordination chemistry with  $\text{Ac}^{3+}$  was probed computationally and with  $\text{Bi}^{3+}$  experimentally via NMR spectroscopy and X-ray crystallography. Furthermore, radiolabeling studies were conducted, revealing the efficient incorporation of both  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$  by py-macroDipa that matches or surpasses the well-known chelators macropa and DOTA. Incubation in human serum at 37 °C showed that  $\sim 90\%$  of the  $^{225}\text{Ac}^{3+}$ –py-macroDipa complex dissociates after 1 d. The  $\text{Bi}^{3+}$ –py-macroDipa complex possesses remarkable kinetic inertness reflected by an EDTA transchelation challenge study, surpassing that of  $\text{Bi}^{3+}$ –macropa. This work establishes py-macroDipa as a valuable candidate for  $^{213}\text{Bi}^{3+}$  TAT, providing further motivation for its implementation within new radiopharmaceutical agents.

Targeted alpha therapy (TAT) is a promising therapeutic strategy that leverages  $\alpha$ -particle-emitting radionuclides to annihilate tumor cells. Compared to conventional internal radiotherapy using  $\beta$ -particle emitters, the implementation of significantly more massive  $\alpha$  particles, which deposit their energy over much shorter distances, provides key advantages. The short range of  $\alpha$  radiation can yield enhanced selectivity for targeted cancer cells, while minimizing damage to surrounding healthy cells. Moreover, the very large linear energy transfer (LET) of  $\alpha$  particles is significantly more effective in causing lethal DNA double strand breaks that kill cancer cells in a more efficacious manner compared to the lower-LET  $\beta$  particles.<sup>1–6</sup>

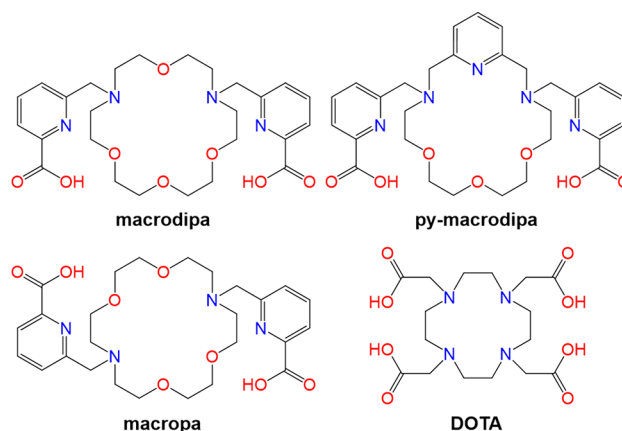
To date, over eight radionuclides have been identified as potential candidates for use in TAT based on their decay properties and production routes.<sup>7</sup> Among these nuclides,  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$  have received considerable attention that has manifested in clinical studies.<sup>8–10</sup>  $^{225}\text{Ac}$  ( $t_{1/2} = 9.9$  d) emits four  $\alpha$  particles through its decay chain, a property that confers it with high cytotoxic potency. Its 9.9-day half-life is also well matched with the in vivo circulation timescales of macromolecular targeting vectors like antibodies.<sup>11,12</sup>  $^{213}\text{Bi}$  ( $t_{1/2} = 45.6$  min), a daughter of  $^{225}\text{Ac}^{3+}$ , emits one  $\alpha$  particle through its decay chain and can be conveniently obtained from  $^{225}\text{Ac}/^{213}\text{Bi}$  generators.<sup>13</sup> Its shorter half-life can be optimally matched to small-molecule targeting vectors, rendering it useful for different systems than those employed for  $^{225}\text{Ac}^{3+}$ .<sup>14,15</sup>

To convert these promising radionuclides into radiotherapeutic agents, a chelator that efficiently binds and stably retains them is required.<sup>16,17</sup> The development of chelators for

large metal ions like  $\text{Ac}^{3+}$  and  $\text{Bi}^{3+}$ , however, is challenging, partly because their low charge density weakens electrostatic interactions with ligand donor atoms.

We recently reported a new ligand called macroDipa<sup>18</sup> and its second-generation analogue py-macroDipa<sup>19</sup> (Chart 1). These “macroDipa-type” chelators feature a unique “dual size

**Chart 1. Structures of Chelators Discussed in This Work**



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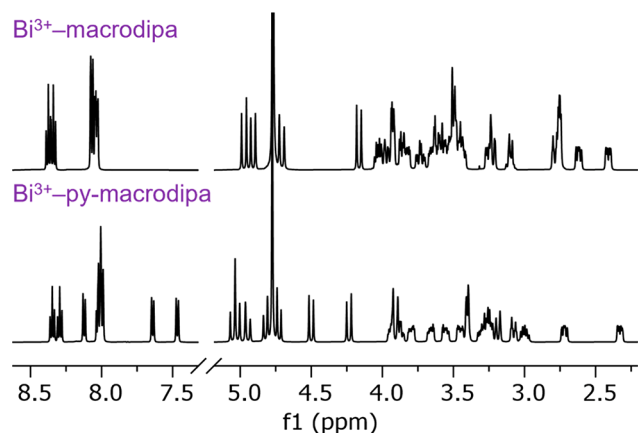
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selectivity”, characterized by their good affinities for both the large and small rare-earth metal ions ( $\text{Ln}^{3+}$ ). This unusual selectivity profile arises from a significant conformational toggle that occurs when they form complexes with  $\text{Ln}^{3+}$  ions of different sizes. Large  $\text{Ln}^{3+}$  form 10-coordinate, nearly  $C_2$ -symmetric complexes (Conformation A), whereas an 8-coordinate, asymmetric complex arises for small  $\text{Ln}^{3+}$  (Conformation B).<sup>18,19</sup> We have further demonstrated that this property makes py-macrodipa a valuable candidate for nuclear medicine applications with both  $^{135}\text{La}^{3+}$  and  $^{44}\text{Sc}^{3+}$ ,  $\text{Ln}^{3+}$  radiometal ions with the largest and smallest ionic radii within this series.<sup>19</sup>

Based on this successful application of macrodipa and py-macrodipa for the  $\text{Ln}^{3+}$  ions, we sought to evaluate these ligands with biomedically relevant ions beyond the  $\text{Ln}^{3+}$  series, namely  $\text{Ac}^{3+}$  and  $\text{Bi}^{3+}$ . The potentials of both chelators for TAT applications using their radioisotopes  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$  were determined and benchmarked to those of the well-known chelators macropa and DOTA (Chart 1), which have established precedence for nuclear medicine applications with these radiometals.<sup>20–23</sup>

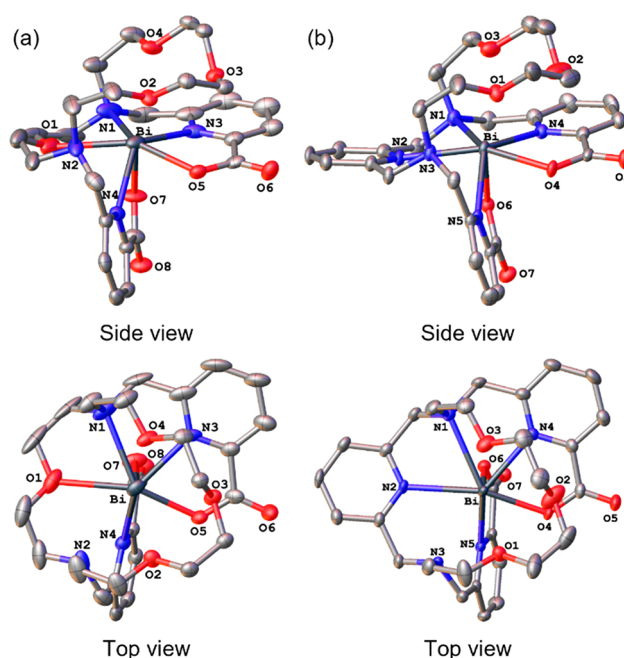
We assessed the coordination chemistry of these ligands with stable  $\text{Bi}^{3+}$ . The  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra of their  $\text{Bi}^{3+}$  complexes ( $\text{Bi}^{3+}$ -macrodipa and  $\text{Bi}^{3+}$ -py-macrodipa) were acquired in  $\text{D}_2\text{O}$  (Figures 1 and S1–S4). These spectra



**Figure 1.**  $^1\text{H}$  NMR spectra of  $\text{Bi}^{3+}$ -macrodipa and  $\text{Bi}^{3+}$ -py-macrodipa (500 MHz,  $\text{D}_2\text{O}$ , pD 5, 25 °C).

reveal the presence of a single, well-resolved species that lacks symmetry for both complexes. Thus,  $\text{Bi}^{3+}$ -macrodipa and  $\text{Bi}^{3+}$ -py-macrodipa most likely attain the asymmetric Conformation B, which is the preferred binding mode of these ligands for small  $\text{Ln}^{3+}$  (Figures S5–S6).

As further validation, we characterized  $\text{Bi}^{3+}$ -macrodipa and  $\text{Bi}^{3+}$ -py-macrodipa by X-ray crystallography (Figure 2). The crystal structures of these complexes confirm that they attain the asymmetric Conformation B, consistent with our observations from NMR spectroscopy. Like their NMR spectra, these  $\text{Bi}^{3+}$  structures are comparable to those of the small  $\text{Ln}^{3+}$  analogues,  $\text{Lu}^{3+}$ -macrodipa and  $\text{Sc}^{3+}$ -py-macrodipa, with respect to the orientation of the picolinate donors and the lack of full engagement of all six macrocycle donor atoms.<sup>18,19</sup> A key difference between these  $\text{Ln}^{3+}$  and  $\text{Bi}^{3+}$  structures, however, is the absence of a coordinated water molecule in the latter. This void is most likely a consequence of the stereochemical activity<sup>24,25</sup> of the  $\text{Bi}^{3+}$   $6s^2$  lone pair. These observations that  $\text{Bi}^{3+}$ -macrodipa and  $\text{Bi}^{3+}$ -py-macro-



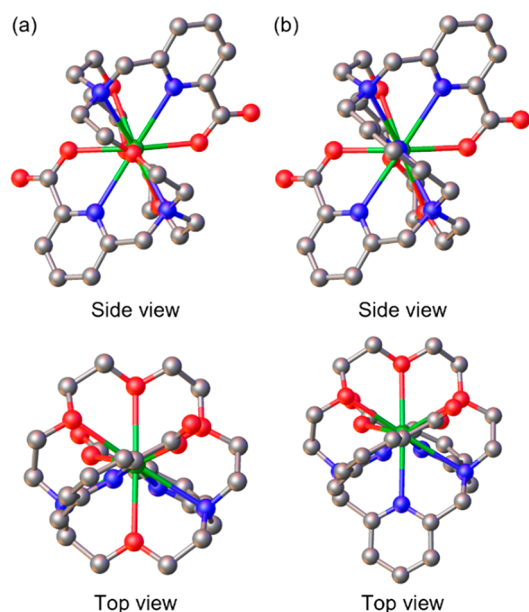
**Figure 2.** Crystal structures of (a)  $[\text{Bi}(\text{macrodipa})]^+$  and (b)  $[\text{Bi}(\text{py-macrodipa})]^+$ . Thermal ellipsoids are drawn at the 50% probability level. Solvent and counterions are omitted for clarity.

dipa attain the asymmetric Conformation B rather than the symmetric Conformation A is somewhat surprising based on the similar ionic radii of  $\text{Bi}^{3+}$  and  $\text{La}^{3+}$ ,<sup>26,27</sup> a representative large  $\text{Ln}^{3+}$ . This result suggests that the stereochemical activity of the  $6s^2$  lone pair plays a pronounced role in mediating the preferred conformations of these  $\text{Bi}^{3+}$  complexes.

Experimental characterization of  $\text{Ac}^{3+}$  complexes is challenging due to the high radioactivity and extremely limited availability of its longest-lived isotope  $^{227}\text{Ac}$  ( $t_{1/2} = 21.8$  y).<sup>28</sup> Thus, we instead probed the structures of  $\text{Ac}^{3+}$ -macrodipa and  $\text{Ac}^{3+}$ -py-macrodipa computationally using density functional theory (DFT) with *Gaussian 16*.<sup>29</sup> The hybrid TPSSH functional,<sup>30</sup> which has been validated for studying  $\text{Ac}^{3+}$  chemistry,<sup>31,32</sup> was adopted. A large-core relativistic effective core potential (LCRECP) and the associated basis set was assigned to the  $\text{Ac}^{3+}$  center,<sup>33–35</sup> whereas the 6-31G(d,p) basis set<sup>36,37</sup> was applied to all other lighter atoms. Aqueous solvation effects were accounted for with the SMD solvation model.<sup>38</sup>

Because the ionic radii and coordination chemistry of  $\text{Ac}^{3+}$  and  $\text{La}^{3+}$  are similar,<sup>28</sup> we optimized  $\text{Ac}^{3+}$ -macrodipa and  $\text{Ac}^{3+}$ -py-macrodipa starting from the geometries of the corresponding  $\text{La}^{3+}$  complexes, which attain the symmetric Conformation A.<sup>18,19</sup> Within these structures (Figure 3), the Ac–O interatomic distances are 2.45–2.48 Å for negatively charged O and 2.70–2.79 Å for neutral O, whereas the Ac–N interactions range from 2.76–2.92 Å. These calculated distances are close to experimentally measured Ac–O and Ac–N interatomic distances.<sup>39–43</sup> Additionally, we optimized both complexes in Conformation B. Consistent with our expectations, Conformation B is energetically disfavored for both complexes (Table S2).

Having established the coordination chemistry of these ligands, we next carried out radiolabeling studies to evaluate their potential value for  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$  TAT in comparison to the state-of-the-art chelators macropa and DOTA. These



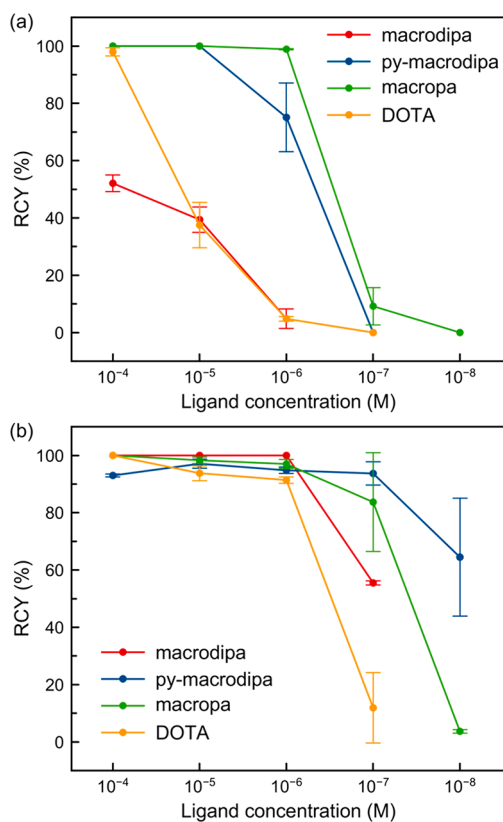
**Figure 3.** DFT-optimized structures of (a)  $[\text{Ac}(\text{macrodipa})]^+$  and (b)  $[\text{Ac}(\text{py-macrodipa})]^+$ . Hydrogen atoms are omitted for clarity. Green: Ac. Gray: C. Blue: N. Red: O.

radionuclides were produced and purified according to previously described protocols.<sup>44–46</sup>

Different concentrations of macrodipa, py-macrodipa, macropa, and DOTA were combined with pH 5.5–6 buffered solutions containing either 20–40 or 30–300 kBq of  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$  at ambient or elevated temperature, and the radiochemical yields (RCYs) were determined by radio-TLC. The concentration-dependent RCYs for these four chelators are summarized in Figure 4. For both radionuclides, py-macrodipa is able to achieve significantly higher RCYs than its analogue macrodipa and the conventional chelator DOTA, which also required high temperatures for radiolabeling. RCYs of approximately 75% and 65% are obtained when using low py-macrodipa concentrations of  $10^{-6}$  M and  $10^{-8}$  M for  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$ , respectively. With respect to  $^{225}\text{Ac}^{3+}$  chelation, py-macrodipa was slightly less effective than macropa, but was better at radiolabeling  $^{213}\text{Bi}^{3+}$ . We also performed  $^{225}\text{Ac}^{3+}$  radiolabeling with macrodipa and py-macrodipa at pH 7 (Table S3). Under this condition, both chelators were able to access greater RCYs, but still failed to surpass macropa. Overall, these studies show that py-macrodipa effectively radiolabels both  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$  under mild conditions.

We next assessed the kinetic inertness of  $^{225}\text{Ac}^{3+}$ –py-macrodipa by incubating it in human serum at 37 °C (Table S5). These studies show that  $^{225}\text{Ac}^{3+}$ –py-macrodipa is fairly labile, as ~90% of the complex dissociated after 1 d. By contrast,  $^{225}\text{Ac}^{3+}$ –macropa remained 98% intact in human serum after 5 d. This excellent kinetic inertness is consistent with a previously reported serum challenge on  $^{225}\text{Ac}^{3+}$ –macropa.<sup>20</sup> Hence, despite the efficient radiolabeling properties of py-macrodipa, it is not an optimal candidate for TAT applications with  $^{225}\text{Ac}^{3+}$ .

Because  $^{213}\text{Bi}^{3+}$  decays quickly ( $t_{1/2} = 45.6$  min), probing the  $^{213}\text{Bi}^{3+}$  complex kinetic inertness by this serum challenge assay is impractical. Instead, we performed a transchelation challenge assay<sup>19–21,47–49</sup> on the macrodipa, py-macrodipa, and macropa



**Figure 4.** Radiochemical yields at different ligand concentrations. (a) RCYs of  $^{225}\text{Ac}^{3+}$  radiolabeling (25 °C for py-macrodipa, macropa, 40 °C for macrodipa, and 80 °C for DOTA; pH 5.5–6; 60 min reaction time). (b) RCYs of  $^{213}\text{Bi}^{3+}$  labeling (25 °C for macrodipa, py-macrodipa, macropa and 95 °C for DOTA; pH 5.5–6; 6–8 min reaction time). Error bars represent the standard deviations. The  $^{213}\text{Bi}^{3+}$  data with macropa and DOTA was taken from ref 21.

complexes with stable  $\text{Bi}^{3+}$ . The transchelation reactions of these  $\text{Bi}^{3+}$  complexes were monitored by UV–Vis spectroscopy in the presence of a 10-fold excess EDTA, a ligand with high affinity for  $\text{Bi}^{3+}$ ,<sup>50,51</sup> at pH 5.0 and 25 °C. Under this condition, the  $\text{Bi}^{3+}$  ion is transchelated by EDTA, following pseudo-first-order kinetics. The resulting half-lives ( $t_{1/2}$ ) for this transchelation process, a comparative measure of complex kinetic inertness, are shown in Table 1.  $\text{Bi}^{3+}$ –macrodipa is kinetically

**Table 1.** Half-Lives of  $\text{Bi}^{3+}$  Complexes when Challenged with 10 Equivalents of EDTA<sup>a</sup>

	$t_{1/2}$
$\text{Bi}^{3+}$ –macrodipa	$9.2 \pm 0.1$ min
$\text{Bi}^{3+}$ –py-macrodipa	$13.2 \pm 1.2$ d
$\text{Bi}^{3+}$ –macropa	$2.2 \pm 0.2$ d

<sup>a</sup> $[\text{BiL}] = 100 \mu\text{M}$ , pH 5.0, 25 °C.

labile to this transchelation challenge. The kinetic inertness of  $\text{Bi}^{3+}$ –py-macrodipa is remarkably enhanced, as reflected by a  $t_{1/2}$  of 13 d. Moreover, its inertness is greater than that of  $\text{Bi}^{3+}$ –macropa, indicating that py-macrodipa is a promising candidate for TAT applications with  $^{213}\text{Bi}^{3+}$ .

In summary, we evaluated the viability of macrodipa and py-macrodipa as chelators for  $^{225}\text{Ac}^{3+}$  and  $^{213}\text{Bi}^{3+}$ . Their coordination chemistry with  $\text{Ac}^{3+}$  and  $\text{Bi}^{3+}$  were characterized computationally and experimentally, respectively. Our radio-



labeling studies revealed that py-macrodipa is highly effective at radiolabeling both radiometals, outperforming both macrodipa and DOTA. Although the lability of  $\text{Ac}^{3+}$ -py-macrodipa precludes its use with  $^{225}\text{Ac}^{3+}$  in nuclear medicine, the efficient formation and high stability of  $\text{Bi}^{3+}$ -py-macrodipa, which surpasses  $\text{Bi}^{3+}$ -macropa, suggests that this ligand is a valuable candidate for  $^{213}\text{Bi}^{3+}$  chelation. These results highlight that py-macrodipa joins other promising candidates for  $^{213}\text{Bi}^{3+}$  chelation that have arisen in recent years.<sup>21,52–60</sup> Ongoing work is directed toward the synthesis of a bifunctional analogue of py-macrodipa to apply this chelator in TAT, as well as the development of “macrodipa-type” chelators with enhanced  $\text{Ac}^{3+}$  complex stabilities.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.inorgchem.1c03670>.

Experimental procedures and supplementary data (PDF)

Geometry outputs for DFT-optimized structures (ZIP)

### Accession Codes

CCDC 2124116–2124117 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare the following competing financial interest(s): J. J. Wilson and A. Hu have filed a provisional patent on the py-macrodipa chelator for nuclear medicine applications.

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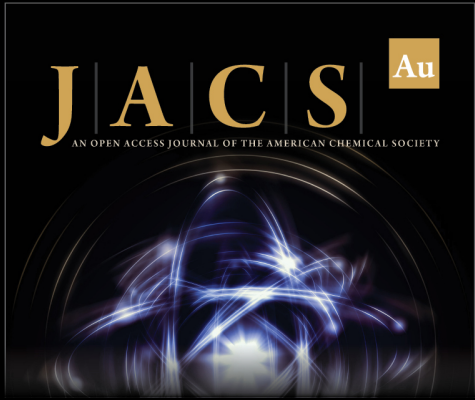
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