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Complexes of copper and bismuth cations with acyclic and macrocyclic polyamines bearing picolinic pendant arms

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By this time acyclic and macrocyclic ligands with picolinate moieties became very attractive for binding of Pb2+, Bi3+, REE3+ and Cu2+. As soon as linear and cyclic ligands are already used in radiopharmaceuticals and characterized by different benefits and drawbacks we decided to evaluate both types with the same set of picolinic arms. Here we present our first results on complexation of cations with new ligands possessing picolinate arms L1-L4.

All ligands were characterized by NMR-spectroscopy, elemental analysis and potentiometric titration. For complex stability study with Bi3+, Cu2+ and Pb2+ potentiometric titration and competitive extraction technique with radioactive tracer were used. Labeling experiments with radioisotopes of 61,64Cu and 207Bi were performed for leading compounds. Dissociative stability of formed complexes in presence of biologically relevant cations as well as rechelation of radionuclides by serum proteins was studied. Control of labeling efficiency and dissociation of complexes was carried out by thin layer chromatography and protein precipitation accompanied by gamma-spectrometry.
Obtained results show lower protonation constants of macrocyclic ligands obviously because of presence of carbamide groups. However complexation constants with Cu2+ and Bi3+ for L4 reach quite high values logK=14.6 and 19.6 respectively. Leading complexes with Cu2+ and Bi3+ possess logK=18.7 and 27.7 for L3. The latter characterized by the largest number of donor atoms and absence of amide groups in contrast to L4 demonstrates the most promising complexation ability. Conditions for effective labeling of L3 by 61,64Cu and 207Bi were determined and synthesized complexes were challenged with excess of Ca2+, Fe3+, Zn2+, stable Cu2+ and serum proteins. It was shown that for >95% radiolabeling yield of L3 and L4 by 207Bi is achieved at c(L)=0.4 mM and 1mM and by 61,64Cu at c(L)=0.2 mM for both ligands. BiL3 and BiL4 in presence of serum proteins have shown slow transchelation up to 40% in 1 hour and to 50-60% in 16 hours. It should be noted that acyclic ligand L3 releases cation much faster and it could be the sequence of well-known tendency of linear ligands to form kinetically unstable complexes. Summarizing all obtained results we can conclude that novel picolinate-containing ligands form complexes almost immediately at room temperature and formed complexes demonstrate stability in vitro.
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