Abstract

In an effort to increase the thermodynamic stability and the kinetic inertness of the complexes, the five new azamacrobicyclic ligands derived from TACN, cyclen, and cyclam have been prepared. The ligands were decorated with phosphinate or phosphonate pendant arms to maintain fast complexation. Since the ascending importance of targeted diagnostic and therapy, the bone-targeted non-bridged cyclam derivative with phosphinate-bis(phosphonate) pendant arm (H_5**TE1P^{BP}**) has also been synthesized. The ligands were studied with respect to their application. The bridged TACN (H_2**bpbtacn**) and cyclen (H_4**bpbcen**) ligands show high macrocyclic basicity (logK_1 = 12.25 and 12.70, respectively). The thermodynamic stability of H_2**bpbtacn** with Cu(II) ion is more than ten orders of magnitude lower than that of the NOTA ligand. The stability constants of H_4**bpbcen** with Cu(II) and Zn(II) ions are comparable to those given for the DOTA. The stability of Ln(III)-**bpbcen** complexes is 7–10 orders of magnitude lower compared to DOTA complexes. For both ligands, the lower thermodynamic stability of the complexes is attributed to the high rigidity of the ligand structure. The bridged cyclam derivatives with phosphonate (H_4**TE2P**), bis(phosphinate) (H_4**TE2bpin**), or phosphinate (H_2**TE2P^{H}**) pendants are characterized by high stability of Cu(II) complexes (log$K$ = 23.97, 20.21 and 21.28, respectively) and high kinetic inertness ($t_{1/2}$ = 120 h, 11 h and 111 h, respectively; 1 M $HClO_4$, 90 °C). The formation kinetics of H_4**TE2P** and H_4**TE2bpin** derivative is very fast and the Cu(II) complexes are quantitatively formed in 2 s at pH ~6 and millimolar concentration. The non-bridged ligand H_5**TE1P^{BP}** is characterized by high macrocycle basicity (logK_1 < 13) and high selectivity for Cu(II) over Zn(II) and Ni(II) ions. The formation of the copper complex is very fast with a quantitative formation of the complex within 1 s (pH ~6, 0.05 mM). The complex is highly inert to acid-assisted decomplexation ($t_{1/2}$ = 1.4 min; 1 M $HClO_4$, 90 °C). Radiolabeling of H_5**TE1P^{BP}** is fast and effective with a specific activity ~30 Bq/μmol (pH 5.5, 25 °C) and the Cu(II) complex shows high affinity to hydroxyapatite in vitro and to bones in vivo. PET experiments in healthy mice and also in direct comparison with [^{18}F]fluoride in a rat femur defect model demonstrate the excellent suitability of H_5**TE1P^{BP}** as copper izotope carrier for imaging active bone compartments.