Complexation of Iron(III) by Phosphonocarboxylate Ligands

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The serum iron transport protein transferrin is a potential target for chelating agents used to treat the iron overload associated with diseases such as β-Thalassemia. However, the kinetics of iron release from this protein are often quite slow. We have recently shown that the rates of iron release by phosphonocarboxylates are relatively rapid (Harris et al., J. Inorg. Biochem. 2004, 98:1824). The present study evaluates the iron-binding affinities of this class of ligands.

The complexation of iron(III) by phosphonoacetic acid (PAA), 2-ethylphosphonoacetic acid (EPAA), phosphonosuccinic acid (PSA), and pyrophosphate (PP_i) has been studied by potentiometric titration and spectrophotometric competition versus desferrioxamine B (DFO). Potentiometric titrations indicate that at 2:1 and 3:1 ligand:metal ratios, all four ligands form bis(ligand) complexes. However, precipitation of metal-ligand species over various pH ranges limits the use of this method to determine formal stability constants. No precipitation is observed during the titrations of Fe(III) with the tridentate ligand phosphonosuccinate (PSA), and the potentiometric data have been used to determine binding constants of log K_1 = 14.94 and log K_2 = 21.27 for the FeL and FeL_2 complexes.

Binding affinities of all the ligands were evaluated by spectrophotometric competition against the siderophore DFO. Because of the high stability of ferric-DFO, a large excess of the phosphonocarboxylate ligands was required. The results showed that at pH 6.2, both PAA and EPAA form tris complexes, while PP_i forms a bis complex. Competition studies with PSA at pH 7 showed that it also forms a tris complex. Effective binding constants determined from the spectrophotometric studies were used to calculate pM values for solutions of 0.3 mM Fe and 100 mM ligand. The pM values are 21.97 for PP_i, 20.2 for PAA, 19.40 for EPAA and 22.8 for PSA. Thus the bidentate ligands PAA and EPAA are weaker binding agents than PP_i, but the tridentate ligand PSA has a binding affinity that is comparable to PP_i.