The use of methanol solutions makes possible the observation of the direct metal AT interaction before ligand decomposition. The X-ray and spectroscopic studies have shown that in both ligands the major coordination site is a heterocyclic nitrogen (for TP see also [6]).

This similarity in metal ion binding by the heterocyclic nitrogen donor of both ligands and their possible chemical analogues could play a critical role in complex formation in a lipid environment.

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PLED – A New Chelating Ligand for the Treatment of β-Thalassemia

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The structure of EDTA has been modified by replacing two acetate groups with *o*-hydroxybenzyl groups, producing N,N′-bis-*o*-hydroxybenzylethylenediamine-N,N′-diacetic acid (HBED) [1] which has a very high affinity for the Fe(III) ion. Previously, an analogous ligand, ethylenebis-*o*-hydroxybenzylglycine (EHPG) had also been reported to have high selectivity for Fe(III) [2]. This paper describes a new ligand analogous to HBED, with pyridine rings derived from vitamin B_6. This ligand, N,N′-dipyridoxylethylenediamine-N,N′-diacetic acid, PLED *1*, has lower pK's than do HBED and EHPG. The corresponding protonation constants of these three ligands, and of EDTA, are presented in Table I. The stability constants of the chelates of PLED with Fe^{3+} and Ga^{3+} are considerably lower than those of HBED and EHPG, and lower than expected on the basis of ligand basicity perhaps because of the steric factors arising from the substituents on the pyridoxyl rings. The much higher stability of the Cu(II) chelate relative to those of EHPG and HBED was unexpected, but the lower coordination requirement of Cu(II) would probably tend to minimize steric repulsions.

PLED, HBED, and EHPG, and their esters have proved to be effective in test animals for the removal of iron overload [4], thus demonstrating the effectiveness of aromatic hydroxyl groups in the design of chelating agents having specificity for Fe(III). The lower stability constant of PLED for Fe(III) is partially compensated for by lower basicity of its donor groups, thus increasing its relative effectiveness at physiological pH. The application of this ligand to the treatment of β-thalassemia is made somewhat attractive by the relatively low toxicity of the pyridoxyl rings.

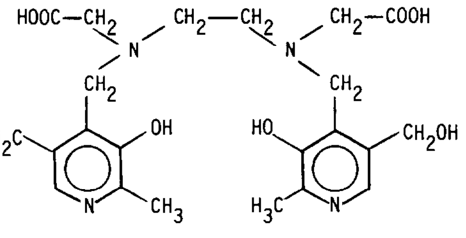

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TABLE I. Protonation Constants and Stability Constants of N,N′-Dipyridoxylethylenediamine-N,N′-diacetic Acid (PLED) and Related Ligands.

Equilibrium Quotient	PLED	HBED [1]	EHPG [2]	EDTA [3]
$[HL]/[L][H]$	11.08	12.46	11.68	10.17
$[H_2L]/[HL][H]$	9.95	11.00	10.24	6.11
$[H_3L]/[H_2L][H]$	8.57	8.32	8.64	2.68
$[H_4L]/[H_3L][H]$	6.26	4.64	6.32	1.95
$[CuL]/[Cu][L]$	26.48	21.38	23.94	18.70
$[FeL]/[Fe][L]$	29.80	39.57	33.9	25.0
$[GaL]/[Ga][L]$	30.45	39.57	33.6	21.0