Very Strong and Selective Complexation of Small Metal Ions by a Highly Preorganised Open-chain Bispidine-based Ligand

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Synthesis of 3,7-bis(2-pyridylmethyl)-3,7-diazabicyclo[3.3.1]nonane DPB, with very rigid nitrogen-bridge reinforcement gives an adamantane-like structure once a metal ion is coordinated to DPB, and shows how remarkable stability enhancement and selectivity for metal ions on the basis of size can be achieved in non-macrocyclic ligands.

The extra thermodynamic stability of complexes of metal ions with macrocyclic ligands as compared with their open-chain analogues is one of the most striking properties of macrocyclic ligands, called the macrocyclic effect.[1] Table 1 shows how the protonation constants of cyclam (see Fig. 1 for ligand structures), and its formation constant[2] with Cu^{II} are enhanced, compared to those of the open chain analogue 2,3,2-tet. In terms of preorganisation,[3] it is not necessary to have a cyclic ligand structure, but simply to constrain the ligand more closely to those conformations required for complexing the target metal ion. Greater preorganisation leads not only to greater thermodynamic stability of the complex formed, but also leads to much greater selectivity[4] for the target metal ion if tailored to fit the coordination geometry needs of such an ion. Such greater preorganisation can be of considerable value in biomedical applications[5] ranging from the design of imaging agents[6] to the development of cancer therapeutic agents containing radioisotopes.[7]

We have sought to design such ligands, where a more rigid bridge between two of the donor atoms would lead to greater preorganisation.[8] Bridges such as the piperazine or diazacyclooctane (DACO) bridge, lead to no enhancement in complex stability compared to non-reinforced ligands.[8] This is due to low levels of preorganisation, since these bridges lead to high steric energy in the conformations requried for coordinating metal ions. Thus, the piperazine group adopts a chair conformation in the free ligands in which it occurs, *ca.* 30 kJ mol^{-1} lower in energy[7] than the boat conformer required to coordinate metal ions. Only when the piperazine bridge is incorporated into a macrocycle where it is constrained to adopt the boat conformer is a large stabilisation observed.[9] Similarly, the DACO bridge is sterically strained when coordinated to a metal ion, and adopts conformations other than those required for coordination as a free ligand.[8]

The bispidine group (Fig. 1) is very rigid, and once a metal ion is coordinated to it, resembles the rigid adamantane molecule. The bispidine group should lead to high levels of preorganisation, particularly for coordination to small metal ions. The metal ion is part of two fused six-membered chelate rings once coordinated to a bispidine group. Since six membered chelate rings lead to selectivity for small metal ions,[10] ligands containing the bispidine group should coordinate small metal ions selectively. The ligand DPB (Fig. 1) was synthesized as outlined in Scheme 1. The protonation constants were determined from the variation of the absorbance of the ligand in the 275 nm region of the electronic spectrum as a function of pH. Three protonation constants of 13.1(1), 4.45(5), and 0.7(1) were found in 0.5 mol dm^{-3} NaCl at 25 °C. The formation constant of DPB with Cu^{II} was determined from the variation of intensity of the d–d band in the copper complex at 598 nm as a function of pH.

Table 1 shows that the increase in protonation constant of DPB compared to the unreinforced analogue DPTN is 4.8 log units, which is a considerably larger effect than found for the macrocyclic effect in cyclam of only 1.41 log units increase in pK compared to 2,3,2-tet. The highly preorganised structure of the bispidine bridge has produced a 'proton sponge'. (It might be thought that such a high first pKa for DPB would make the ligand an inefficient complexing agent, but subsequent protonation constants are so low for DPB that it is much more efficient than DPTN.) The increase in log K_1 for Cu^{II} is

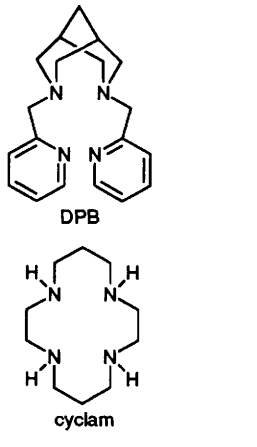
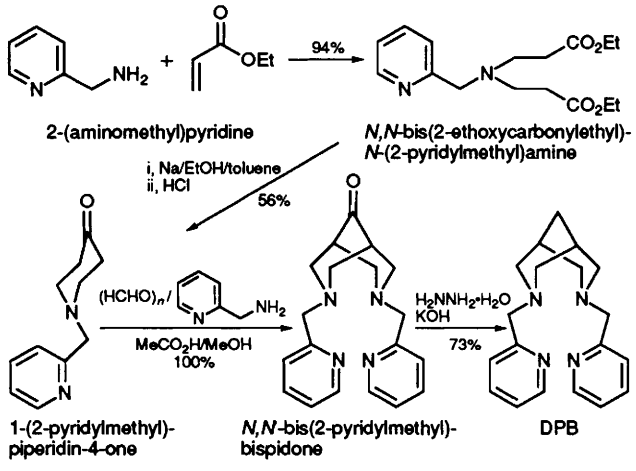


Fig. 1



Scheme 1

Table 1 The thermodynamic effect produced by high levels of preorganisation on macrocyclic and structurally reinforced ligands, compared to the analogues without the features leading to the high levels of preorganisation[a]

	Ligand	Preorganised analogue	Extra stabilisation
	2,3,2-tet	cyclam	
pK_1	10.08	11.49	1.41
$\log K_1$ Cu^{II}	23.9	27.2	3.3
	DPTN	DPB	
pK_1	8.33	13.1	4.8
$\log K_1$ Cu^{II}:	18.35	23.0	4.6

[a] Formation constants for 2,3,2-tet, cyclam, and DPTN from ref. 2.

larger for DPB compared to DPTN by 4.6 log units, which is significantly larger than the 3.3 log units of stabilisation observed in the macrocyclic effect.[1] Further, although tetraaza-macrocycles of all cavity sizes form stable complexes with the large Pb^{II} ion, DPB showed no complex formation with Pb^{II} right up to the pH of precipitation of lead hydroxide. This is attributed to strong selection against large metal ions produced by the rigid six membered chelate rings involving the bispidine bridge. These results demonstrate that extremely high levels of preorganisation can be associated with non-macrocyclic ligands, and we have embarked on a programme of synthesis of other ligands containing the bispidine group.

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