

Structurally reinforced macrocyclic ligands

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Abstract -The coordinating properties of structurally reinforced macrocyclic ligands are discussed. The ligand B-12-aneN₄ (1,4,7,10-tetraazabicyclo[8.2.2]tetradecane) has a very small cavity, and is able to compress the low-spin Ni(II) ion. In spite of the resulting high steric strain in [Ni(B-12-aneN₄)]²⁺, the complex is of high stability, because the free ligand itself is also of very high steric strain. In complexes of Cu(II) with unreinforced macrocycles with cavities that are too large for the Cu(II), the Cu-N bonds are not stretched, but rather the coordination geometry of the Cu(II) is distorted toward tetrahedral, and normal Cu-N bonds are found. In contrast, a large cavity reinforced macrocycle such as NE-3,3-HP (11-methyl-11-nitro-1,5,9,13-tetraazabicyclo-[11.3.2]tetradecane) is able to stretch the Cu-N bonds out to 2.09 Å, since the homopiperazine reinforcing bridge prevents buckling of the ligand. However, with further increase in macrocyclic ring size, buckling of the ligand and tetrahedral distortion of the Cu(II) occurs, showing the need for even more rigid reinforcing groups. The synthesis and properties of ligands containing the bispidine group, which has an adamantane-like structure, as a reinforcing group, is discussed.

INTRODUCTION

Over the last few years we have come to the conclusion, based on Molecular Mechanics (MM) (ref. 1-4) and thermodynamic (ref. 5-7) studies, that ordinary macrocyclic ligands are too flexible to show strong size-match selectivity. By size-match selectivity is meant that a metal ion will form its most stable complex with that member of a series of macrocycles where the match between the size of the metal ion, and the size of the cavity in the macrocycle is closest. Since a major aspect of our research is controlling selectivity for the selective removal of toxic metal ions (refs. 8,9), we have sought ways of increasing the rigidity, and therefore, possibly, the selectivity, of macrocyclic ligands.

STRUCTURALLY REINFORCED MACROCYCLES

One approach to improved rigidity lies in *structural reinforcement* of the macrocycle. The first examples of structurally reinforced macrocycles were B-12-aneN₄ and B-14-aneN₄ (Fig. 1), reported by Wainwright *et al.* (refs. 10,11). A point of interest in B-12-aneN₄ was the fact that models showed virtually no space in the centre of the ligand (Fig. 1) for accommodating the metal ion. Wainwright had reported that B-12-aneN₄ formed complexes of low-spin Ni(II) of very high Ligand Field (LF) strength, which was attributed to compression of the Ni(II). The structure of [Ni(B-12-aneN₄)](ClO₄)₂ (ref. 12) showed a very distorted structure with short mean Ni-N bond lengths of 1.86 Å, as compared

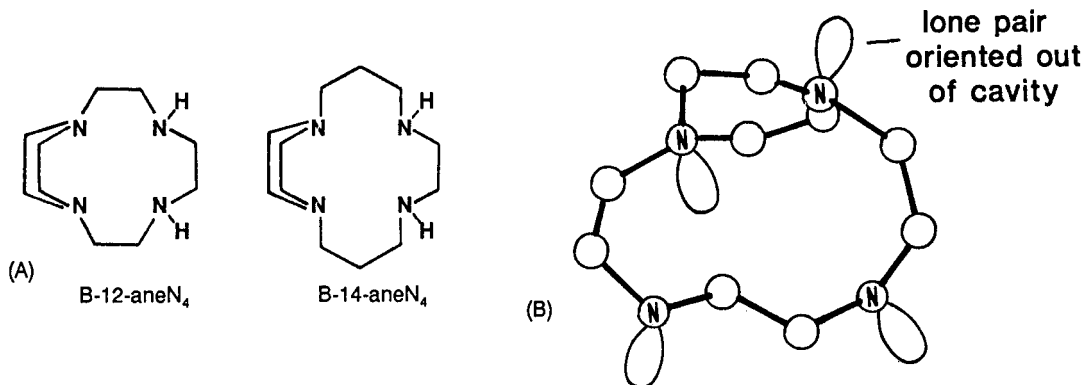


Fig. 1.(A) Structurally reinforced macrocycles;(B) structure of free B-12-aneN₄ generated by molecular dynamics calculation, showing how lone pairs on nitrogen are oriented out of ligand cavity to lessen electrostatic repulsion.

with a Ni-N of 1.92 Å in $[\text{Ni}(\text{EN})_2]^{2+}$. The structure of $[\text{Ni}(\text{B-12-aneN}_4)]^{2+}$ was well reproduced by MM calculations, which supported the idea of compression. Important symptoms of compression of the Ni(II) (Fig. 2) are C-N-C angles forced out to 120° by return pressure from the metal ion, the ejection of the Ni(II) from the plane of the donor atoms, and the forcing of the ethylenes of the piperazine type bridge into an eclipsed conformation.

In view of the highly strained complex with Ni(II), the high thermodynamic stability of the complexes of B-12-aneN₄ with Ni(II) and Cu(II) is surprising. Molecular dynamics studies being carried out by the present authors suggest that the high stability of the highly strained complex derives from the fact that the free ligand B-12-aneN₄ (Fig. 1) is also very highly strained. These complexes also exhibit the largest known macrocyclic effect relative to their open-chain analogue BAE-P; the macrocyclic effect (ref. 13) is the difference in logK_f between the complex of the macrocycle and that of its open chain analogue.

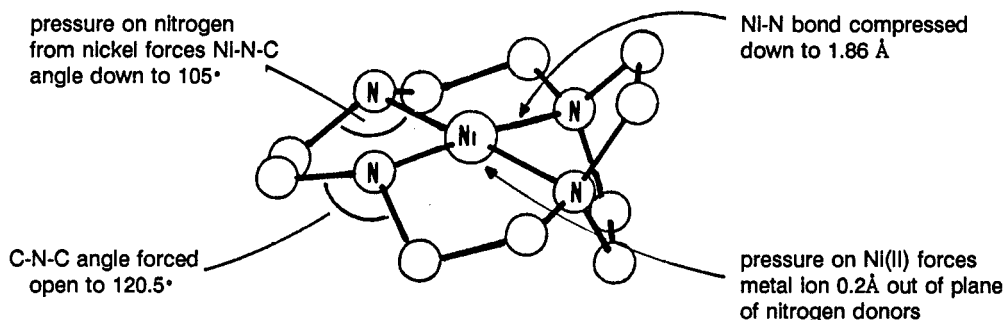


Fig. 2. Structure (ref. 12) of $[\text{Ni}(\text{B-12-aneN}_4)]^{2+}$, showing how compression of the metal ion leads to distortion of the ligand.

THE BASICITY OF THE NITROGEN DONORS IN POLYAMINES

A large amount of evidence (refs. 2,3) shows that the intrinsic basicity of the nitrogen donors in polyamines increases along the series primary < secondary < tertiary. The protonation constants of amines (and other ligands) in aqueous solution are a poor guide to intrinsic basicity, since the strongly solvated proton is highly susceptible to steric hindrance by the alkyl substituents on the donor atom. However, gas-phase protonation energies show (ref. 3) strong increases in basicity with increasing alkyl substitution of amines. Three noticeable effects of the increased basicity of the nitrogens in macrocycles as compared to the open-chain ligands (ref. 3.), summarized in Fig. 3, are 1) increased ligand field (LF) strengths *provided the metal ion can coordinate in a low strain fashion in the cavity in the macrocycle*, 2) increased enthalpy of complex formation, and 3) an increased ability (ref. 14) to stabilize complexes of high oxidation state such as Cu(III) or Hg(III).

One would predict that the change in the nitrogen from secondary to tertiary on reinforcement of the macrocycle would lead to increases in LF strength, and this is what is observed in Fig. 3:

	nitrogens zeroth	primary	secondary	tertiary
$\Delta H [\text{Cu(II)}]$ (kcal.mol ⁻¹)	-22.0	-25.5	-32.4	?
$\chi(\text{d-d})(\text{cm}^{-1})$ Cu(II)	17000	18300	19900	21050
Ni(II)	~ 20000	21600	22470	23900

Fig. 3. The effect of increases in donor strength of the nitrogens along the series primary < secondary < tertiary on LF strength, and on enthalpy of complex formation, in complexes of Cu(II) and Ni(II).

THE RIGIDITY OF THE CAVITY IN REINFORCED MACROCYCLES

Part of the idea of studying reinforced macrocycles is that the cavity in the centre of the ligand should be more rigid than that of conventional macrocycles. This idea is partly supported by a comparison of the Cu(II) complex of NE-3,3,3 (ref. 15) with that of the reinforced NE-3,3-HP (ref. 16). Thus, in the non-reinforced NE-3,3,3 complex the cavity which is too large for the Cu(II) does not (ref. 15) result in significant stretching of the Cu-N bond out towards the best fit Cu-N length of 2.22 Å for the cavity. Rather, the Cu(II) distorts toward a tetrahedral structure, which allows for collapse of the macrocyclic cavity, and preservation of near normal Cu-N bond lengths. In contrast (ref. 16), in the complex of the similar but reinforced macrocycle, the Cu-N bonds are considerably stretched from their ideal length of about 2.0 Å out to 2.09 Å. However, the rigidity of reinforced macrocycles also does not allow unlimited stretching of the Cu-N bond as the macrocyclic cavity. Thus, with addition of one more methylene group to the ring of NE-3,3-HP to give NE-3,3-DAC, as shown in Fig. 4, a collapse of the macrocyclic cavity occurs here too (Fig. 4), with distortion of the coordination geometry around the Cu(II) toward tetrahedral, and maintenance of normal Cu-N bond lengths of 2.01 Å (ref. 17). It is evident from this that possibly even more rigid reinforcing groups might be needed.

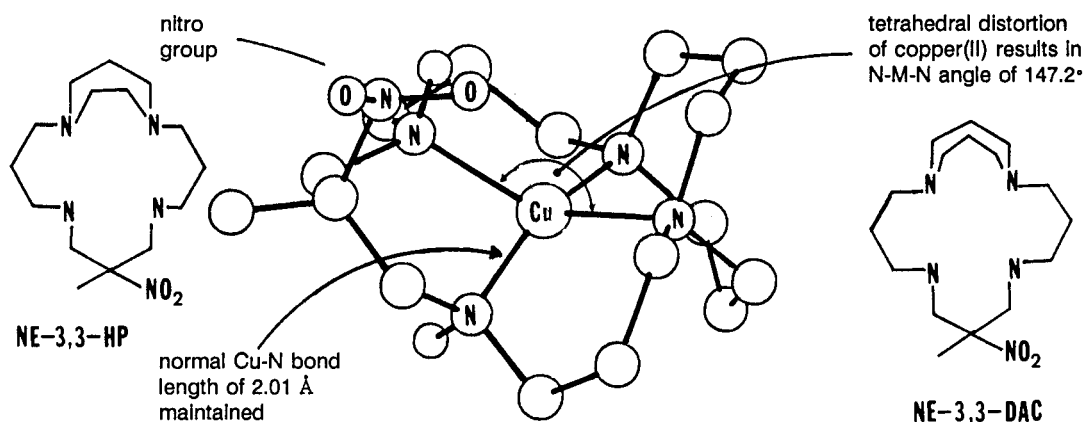


Figure 4. The structure of $[\text{Cu}(\text{NE-3,3-DAC})]^{2+}$, showing how the ligand buckles to give tetrahedral coordination around the Cu(II) ion with maintenance of normal Cu-N bond lengths (ref. 17).

THE NATURE OF THE REINFORCING BRIDGE

A variety of reinforced bridging groups can be used, and as seen in Fig. 5, these can have different requirements in terms of the M-N bond length and N-M-N bond angle which allows coordination with minimum steric strain. Thus, the piperazine type of bridge requires M-N bonds longer than, and an N-M-N angle smaller than, in any known metal ion, which accounts to some extent for its poor coordinating abilities. The homopiperazine group requires a metal ion with far more "normal" geometric requirements, which may point to its extensive use in reinforced macrocycles.

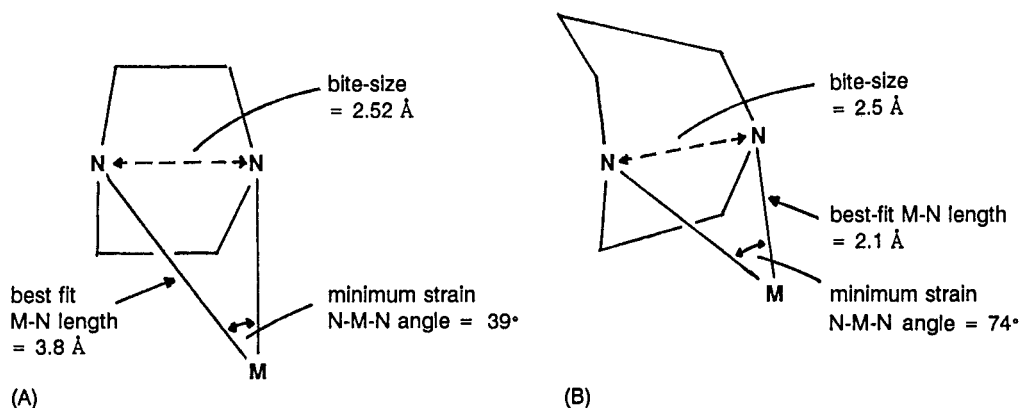


Fig. 5. The requirements in terms of metal ion M-N bond lengths and N-M-N bond angles for coordination with a) piperazine and b) homopiperazine groups.

The collapse of Cu(II) toward tetrahedral coordination geometry as shown in Fig. 4, however, may mean that for truly rigid ligands, even more rigid bridges are required. As shown in Figure 6, the bispidine group resembles adamantane, whose name is derived from "diamond", in that the carbon skeleton of this alkane is like a small piece of diamond.

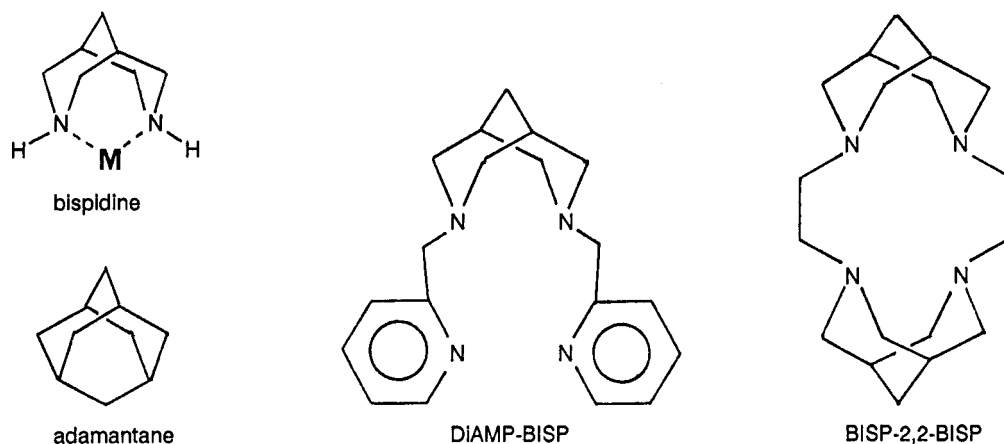


Fig. 6. The extremely rigid ligand bispidine, and its derivatives DIAMP-BISP and BISP-2,2-BISP.

The bispidine ring with its coordinated metal ion resembles adamantane in its potential rigidity. We have thus started on a program to synthesize ligands, both open chain and macrocyclic, that contain the bispidine group. The approach to the synthesis of such ligands involves (ref. 18) preparation of the N-substituted piperidone. For example DIAMP-BISP is prepared from N-(2-pyridylmethyl)-piperidone, and condensation of this with aminomethylpyridine and formaldehyde. The resulting ketone is converted to the bispidine derivative via the Wolff-Kishner reduction. The ligand DIAMP-BISP shows macrocycle-like properties, such as very slow demetallation reactions, as well as high thermodynamic stability towards demetallation. This reflects the high levels of preorganisation imparted to the ligand by the rigid bispidine group. Work is currently in progress on the synthesis of BISP-2,2-BISP, shown in Fig. 6, which molecular mechanics calculations suggest will be of extreme rigidity. It is also anticipated that the presence of four tertiary nitrogens in the ligand BISP-2,2-BISP will lead to in-plane ligand fields of unprecedented strengths, and chemistry of great interest.

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