

Ultra rigid cross-bridged tetraazamacrocycles as ligands—the challenge and the solution

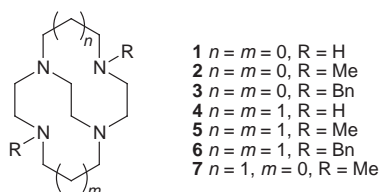
Timothy J. Hubin,^a James M. McCormick,^a Simon R. Collinson,^a Nathaniel W. Alcock^b and Daryle H. Busch^{*a†}

^a Chemistry Department, University of Kansas, Lawrence, KS 66045, USA

^b Chemistry Department, University of Warwick, Coventry, UK CV4 7AL

The challenge to metal ion binding that is represented by the proton-sponge nature of two-carbon cross-bridged tetraazamacrocycles has been overcome and a general method developed for the synthesis of their transition, and other, metal complexes; these ultra-rigid ligands form complexes having remarkable kinetic stabilities.

According to modern coordination chemistry principles,¹ ligands of great rigidity impart enormous kinetic stability to their complexes, and such a property facilitates the exploitation of transition metal ions in biomimicry, catalysis, and numerous other areas. In this context, we have reexamined the cross-bridged tetraazamacrocycles^{2,3} of Weisman and Ciampolini and focus on the *ultra-rigid* two-carbon cross-bridged ligands² 1–7.



These ligands are proton sponges (for **5**, $pK_{a1} > 24$ and $pK_{a2} = 10.8$).² Consequently, in protonic solvents only the proton-like Li^+ ion² and the most strongly binding divalent transition metal ions, Cu^{2+} and Ni^{2+} , form complexes with such ligands.⁴

We have overcome this obstacle; reaction of anhydrous metal salts with strictly deprotonated ligands (distillation from KOH after extraction from $pH \geq 14$ water) in rigorously dry aprotic solvents under a dry, inert atmosphere has yielded the first complexes of a broad array of transition metal ions. With routinely high yields, complexes of Cr^{II} , Mn^{II} , Mn^{III} , Fe^{II} , Fe^{III} , Co^{II} , Ni^{II} , Cu^I , Cu^{II} and Zn^{II} have been obtained.[‡] In many cases, elimination of any source of protons is crucial for complexation. X-Ray crystal structures have been obtained of the Mn^{II} , Mn^{III} , Fe^{II} , Fe^{III} , Co^{II} , Ni^{II} , Cu^I , Cu^{II} and Zn^{II} complexes with ligands having 12- and 14-membered rings and a variety of R groups. In all cases, the ligand is folded, and in most cases it occupies two axial and two *cis* equatorial sites of a distorted octahedra. Exceptions occur with pentacoordinate copper(II) and tetracoordinate copper(I). For complexes of **5**, there is a clear correlation between the ionic radius of the metal ion and the $N_{ax}-M-N_{ax}$ bond angle, which increases smoothly from Mn^{II} through Cu^{II} as the smaller metal ions can more easily be engulfed by the macrobicycle. $Mn^{II}(\mathbf{5})Cl_2$ (Fig. 1) exemplifies these structures,[§] and in this example the $N(3)-Mn(1)-N(4)$ angle is 158.0° .

Because of their great importance in catalysis⁵ and bio-inorganic chemistry,⁶ this report focuses on the manganese, iron and copper derivatives. Magnetic susceptibility data for $[Mn(\mathbf{5})Cl_2]$ indicates that it is high spin d^5 . Accordingly, there are no intense electronic transitions and the X-band EPR spectrum in EtOH at 77 K contains a six-line signal centered at $g = 2.026$. The cyclic voltammogram of $[Mn(\mathbf{5})Cl_2]$ in MeCN

exhibits reversible oxidation-reduction processes at $+0.585$ (Mn^{2+}/Mn^{3+}) and $+1.343$ V (Mn^{3+}/Mn^{4+}) versus SHE that are sensitive to solvent, macrocycle ring size and N-substitution. Since the proton-sponge behavior of the ligands that complicates complexation also interferes with the potentiometric determination of stability constants, other methods have been used to demonstrate the exceptional stabilities of these complexes. $[Fe(\mathbf{2})Cl_2]$ and $[Fe(\mathbf{5})Cl_2]$ show no degradation in either acidic (pH 1) or basic (pH 13) aqueous media in air for periods up to one month. After standing for several weeks in aqueous 2 M NaOH in air at room temperature, $[Mn(\mathbf{5})Cl_2]$ produced a pure Mn^{III} complex and only traces of MnO_2 (probably from unreacted Mn^{2+} impurities).

Copper(II), known for forming the most stable, yet most labile, divalent transition metal complexes, provides a fascinating insight into the stabilities of these ultra-rigid complexes. The UV–VIS spectrum of a 0.1 mM solution of $Cu(\mathbf{5})^{2+}$ in 1 M $HClO_4$ remains unchanged over several weeks at $40^\circ C$; from estimated errors, the lower limit of the half-life for ligand dissociation is > 6 years. This is to be compared with the rate of dissociation of $Cu(tmc)^{2+}$ ($tmc = N,N',N'',N'''$ -tetramethylcyclam) whose ligand is the nearest unbridged structural analogue of **5**. The ligand tmc differs from **5**, hypothetically, by breaking the C–C bridge bond and converting the residual methylenes into methyl groups. The half-life of $Cu(tmc)^{2+}$ at $25^\circ C$ in 1 M HNO_3 is only 2.0 s (calculated from the rate law⁷), at least eight orders of magnitude smaller than that of $Cu(\mathbf{5})^{2+}$. ($> 2 \times 10^8$ s

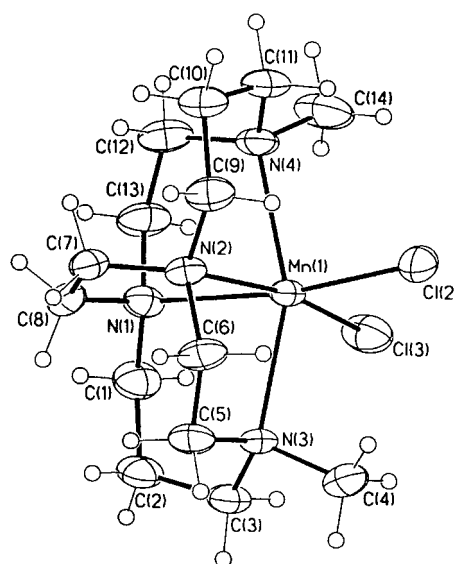


Fig. 1 Molecular structure of $[Mn(\mathbf{5})Cl_2]$. Selected bond lengths (\AA) and angles ($^\circ$): $Mn(1)-N(1)$ 2.347(4); $Mn(1)-N(2)$ 2.332(4); $Mn(1)-N(3)$ 2.325(4); $Mn(1)-N(4)$ 2.333(4); $Mn(1)-Cl(2)$ 2.456(2); $Mn(1)-Cl(3)$ 2.455(2); $N(3)-Mn(1)-N(4)$ $158.0(2)$; $N(1)-Mn(1)-N(2)$ $75.6(2)$; $Cl(2)-Mn(1)-Cl(3)$ $98.85(6)$.

in 1 M HClO₄). The classic example of a kinetically stable Cu²⁺ complex,⁸ Cu(tet-A)²⁺ (tet-A = 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane), provides significant comparisons. Its blue isomer is believed to contain tet-A in the folded form, the same conformation that the bridged cyclam ligand is forced to adopt. This complex, *cis*-Cu(tet-A)²⁺, loses its macrocyclic ligand in 6.1 M HCl with a half-life of about 3 min; replacement of the six *C*-methyls in tet-A by two *N*-methyl groups and the short two-carbon cross-bridge in **5** increases the kinetic stability of the corresponding complex by at least six orders of magnitude. Even the square planar red isomer of Cu(tetA)²⁺ is at least 100 times more labile than the folded bridged cyclam complex Cu(**5**)²⁺. Hence ultra-rigid, cross-bridged tetraazamacrocyclic complexes are indeed ultra-stable, at least in the kinetic sense.

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Notes and References

† E-mail: dbusch@eureka.chem.ukans.edu

‡ *Typical Complexation Reaction* for [Mn(**5**)Cl₂]: All steps were performed in an inert atmosphere glovebox with solvents distilled over CaH₂ and degassed by three freeze/pump/thaw cycles before introduction to the glovebox. To 1.00 g (0.004 mol) of **5** [obtained by literature procedures (ref. 2)] suspended in 40 ml MeCN was added 1.14 g (0.004 mol) Mn(py)₂Cl₂ [obtained by literature procedures (ref.9)] with stirring. The ligand and initially slightly soluble metal source were completely dissolved after 2 h stirring at room temperature. The reaction mixture was allowed to stir an additional 12 h, then filtered. The product was obtained upon evaporation of the solvent. The yield was 1.16 g (77%). The FAB⁺ mass spectrum in MeCN (NBA matrix) exhibited peaks at *m/z* 344 [Mn(**5**)Cl] and 379 [Mn(**5**)Cl₂]. Calc. for Mn(**5**)Cl₂: C, 44.22; H, 7.95; N, 14.73. Found: C, 44.48; H, 7.86; N, 14.98%. Crystals suitable for X-ray diffraction were grown by the slow evaporation of an MeCN solution under an inert atmosphere.

§ *Crystal data* for [Mn(**5**)Cl₂]: C₁₄H₃₀N₄Cl₂Mn, *M* = 380.26, green-yellow badly-formed blocks, crystal dimensions 0.38 × 0.20 × 0.18 mm, monoclinic, space group *P*2(1)/*c*, *a* = 8.2967(2), *b* = 13.9194(4), *c* =

15.9010(5) Å, β = 100.6210(10)°, *V* = 1804.87(9) Å³ (by least squares refinement on 4500 reflection positions), *Z* = 4, *T* = 293(2) K, *D_c* = 1.399 g cm⁻³, Mo-Kα radiation (0.71073 Å), μ(Mo-Kα) = 1.027 mm⁻¹, *F*(000) = 804, Siemens SMART three-circle system with CCD area detector. Maximum θ was 28.35°, *hkl* ranges were -11/10, -18/18, -10/20. Absorption correction by ψ-scan; crystal decay compensated for in data processing. The structure was solved by direct methods using SHELXS (TREF) with additional light atoms found by Fourier methods. Heavy atoms were located by the Patterson interpretation section of SHELXS and the light atoms then found by E-map expansion and successive Fourier syntheses. Refinement used SHELXL 96. Hydrogen atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl hydrogen atoms) times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached. Goodness-of-fit on *F*² was 1.133, *R*₁ = 0.0819 for 2710 reflections with *I* > 2σ(*I*), *wR*₂ = 0.2228, 10463 measured reflections, 4145 unique reflections [*R*(int) = 0.1040], number of refined parameters 192, largest difference peak and hole 1.153 and -1.259 e Å⁻³.

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