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Allosteric Effects in a Ditopic Ligand Containing Bipyridine and Tetra-aza-crown Donor Units

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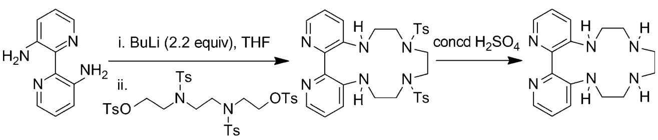
Interest in artificial allosteric systems is largely due to the importance of allostery in regulating the catalytic activity of enzymes. Artificial allosteric systems are often ditopic ligands, molecules that contain two binding sites capable of interacting with other molecular species such as anions and cations.[1] The system is termed allosteric when substrate binding at one site of the ditopic ligand causes conformational changes that modify the properties of the other, chemically remote, site; in other words, the sites are mechanically coupled. A classic example of this is the work of Rebek et al.[1a] They demonstrated that the selectivity of s-block cation transport across a liquid–liquid membrane, by a crown ether unit linked in the 3,3′-positions to 2,2′-bipyridine (bipy), can be tuned by coordination of a d-block metal to the bipy site.[1a] Since then, various other systems have been reported, amongst which are examples of how allostery can regulate overall molecular structure,[2a] binding specificity[2b] and catalytic activity.[3] Despite the impressive efforts undertaken to characterise these systems and their allosteric behaviour, however, structural and thermodynamic rationales for the observed phenomena are often sparse.

In this paper we report the synthesis and coordination properties of a ditopic ligand containing bipy and tetra-aza-crown N-donor units. Both sites complex Cu^{II} dications, but the donor mode of the latter is controlled by the binding state of the bipy unit. An allosteric effect, characterised by negatively cooperative binding of a second Cu^{II} ion, is assigned to the tetra-aza-crown being able to coordinate through only three of its N-donors when the bipy site is occupied.

The ligand L was synthesised in two steps from 3,3′-diamino-2,2′-bipyridine (Scheme 1 and the Supporting Information) and its single crystal X-ray structure determined (Figure 1).[4] In the solid state, the two pyridine rings are twisted, with an NCCN torsion angle of 110(1)°. Steric restraints in the aza-macrocycle prevent these rings from adopting the coplanar *transoid* geometry favoured by bipy systems with hydrogen-bond donors in the 3,3′-position.[5,6]



Scheme 1. Synthesis of ditopic ligand L; Ts = tosyl.

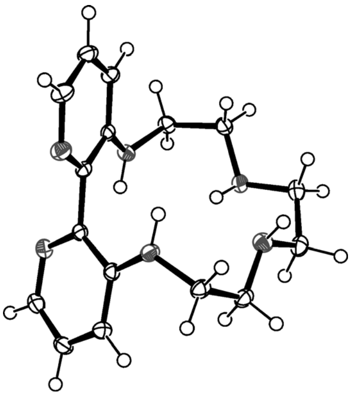


Figure 1. Solid-state structure of the ditopic ligand L.

Spectrophotometric titrations of CuCl$_2$•2H$_2$O into a solution of the ligand ($[L]_{tot} = 10^{-4}$ M, MeCN) caused complex variations in the UV/Vis spectra (see the Supporting Information), which were satisfactorily modelled by the six absorbing species (Cu^{II}, L and four complexes, see Figure 2) in Equations (1), (2), (3) and (4):[7]

$$\mathrm{Cu^{II}}+2\mathrm{L} \Leftrightarrow [\mathrm{Cu(L)_2}]^{2+} \log\beta_{1,2}^{\mathrm{Cu,L}} = 16.8(4) \tag{1}$$

$$\mathrm{Cu^{II}}+\mathrm{L} \Leftrightarrow [\mathrm{Cu(L)}]^{2+} \log\beta_{1,1}^{\mathrm{Cu,L}} = 11.0(4) \tag{2}$$

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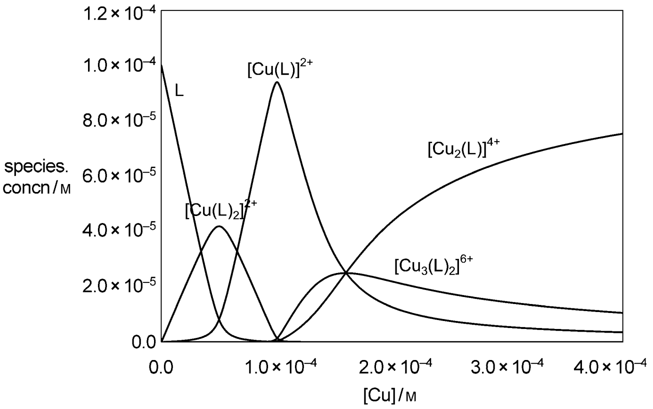

Figure 2. Calculated speciation diagram for complexes of L with $\mathrm{Cu^{II}}$ ($[\mathrm{L}]_{\mathrm{tot}} = 10^{-4}\,\mathrm{M}$).

$$3\mathrm{Cu^{II}}+2\mathrm{L} \Leftrightarrow [\mathrm{Cu_3(L)_2}]^{6+} \log\beta_{3,2}^{\mathrm{Cu,L}} = 31.6(6) \tag{3}$$

$$2\mathrm{Cu^{II}}+\mathrm{L} \Leftrightarrow [\mathrm{Cu_2(L)}]^{4+} \log\beta_{2,1}^{\mathrm{Cu,L}} = 16.0(4) \tag{4}$$

Chloride adducts for all species were observed in the gas-phase during parallel ESI-MS titrations (see the Supporting Information). The formation of four complexes is not unexpected given both 1) the diverse coordination modes a ligand such as L is potentially capable of achieving and 2) the presence of a coordinating solvent (MeCN) and the $\mathrm{Cl^-}$ counterion, which can stabilise coordinatively unsaturated species.

For $[\mathrm{Cu(L)_2}]^{2+}$ we reasonably assume that the $\mathrm{Cu^{II}}$ ion is coordinated by the bipy imine donors of two ligands, whereas in the 1:1 complex $[\mathrm{CuL}]^{2+}$ it is coordinated by the tetradentate aza-crown of one ligand. The structure of the latter complex has been confirmed by an X-ray diffraction study on crystals grown from a solution containing equimolar $\mathrm{CuCl_2{\bullet}2H_2O}$ and L (Figure 3).[8]

The copper ion is indeed coordinated by the four nitrogen atoms of the tetra-aza macrocycle. An axial chloride ligand completes the coordination sphere, giving the $\mathrm{Cu^{II}}$ centre a five-coordinate distorted square-pyramidal geometry. The $\mathrm{Cu{-}N_{aza}}$ bond lengths range from 2.008(2)–2.083(2) Å and the $\mathrm{Cu{-}Cl_{ax}}$ distance is 2.4026(6) Å. A further feature of interest is the bipy NCCN torsion angle, which decreases from 110(1)° in the free ligand to 62(1)°. This reduction occurs so that the amine substituents on the 3,3′-positions of bipy are optimally aligned for binding the metal ion.

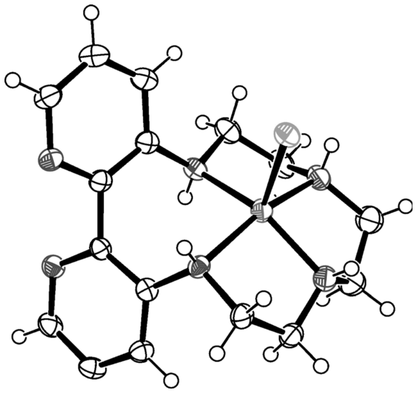

Figure 3. Solid-state structure of the complex cation $[\mathrm{Cu(L)Cl}]^+$.

Reaction of $[\mathrm{Cu(L)Cl}]^+$ with a further equivalent of $\mathrm{CuCl_2{\bullet}2H_2O}$ in MeOH gives a green crystalline solid for which X-ray diffraction shows the dicopper complex $[\mathrm{Cu_2(L)Cl_4}]$ in Figure 4.[9] In the crystal, the ligand coordinates one $\mathrm{Cu^{II}}$ ion through the bipy donor unit and another $\mathrm{Cu^{II}}$ ion through the aza-crown macrocycle. The former is bound by the two nitrogen atoms of bipy ($\mathrm{Cu{-}N_{bipy}}$: 2.056(3) and 2.060(3) Å) and two (roughly) equatorial chloride ligands ($\mathrm{Cu{-}Cl_{eq}}$: 2.296(1) and 2.314(1) Å). The remaining axial site is occupied by a bridging chloride ligand from another molecule of $[\mathrm{Cu_2(L)Cl_4}]$ ($\mathrm{Cu{-}\mu{-}Cl_{ax}}$: 2.742(1) Å), giving rise to a chloro-bridged dimer in the solid state.

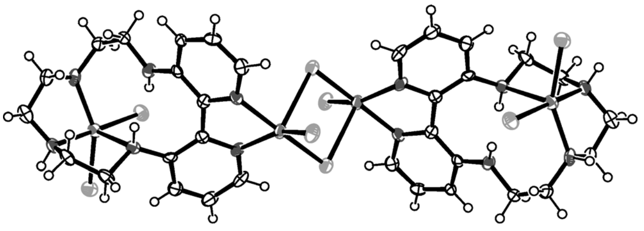

Figure 4. Solid-state structure of the chloro-bridged dinuclear complex $[\mathrm{Cu_2(L)Cl_4}]_2$.

The trinuclear complex $[\mathrm{Cu_3(L)_2}]^{6+}$ implied by the UV/Vis titrations was not characterised in the solid state. However, it was observed in the gas phase. The ESI-MS of a solution containing a 3:2 Cu/L ratio shows an intense peak at *m/z* 964 that corresponds to the complex cation $[\mathrm{Cu_3(L)_2Cl_5}]^+$ (see the Supporting Information). We suspect that it is structurally related to the $[\mathrm{Cu_2(L)Cl_4}]$ complex: instead of being a chloro-bridged dimer, however, two $[\mathrm{Cu(L)Cl}]^+$-type complexes are held together by interaction of the four bipy N-donors with a central $\mathrm{Cu^{II}}$ ion. The aza-crown-bound $\mathrm{Cu^{II}}$ ion of $[\mathrm{Cu_2(L)Cl_4}]$ (and presumably $[\mathrm{Cu_3(L)_2Cl_5}]^+$) is again five-coordinate, but it acquires its distorted square pyramidal geometry from three nitrogen atoms in the aza-crown and two chloride ions. The aza-crown therefore now acts as a tridentate donor. The two "outer" aza nitrogen atoms and the two chloride ligands lie roughly in an equatorial plane ($\mathrm{Cu{-}N_{aza}}$: 2.021(3) and 2.088(3) Å; $\mathrm{Cu{-}Cl_{eq}}$: 2.281(1) and 2.359(1) Å). One of the "inner" aza nitrogen atoms lies in the elongated axial position ($\mathrm{Cu{-}N_{aza}}$: 2.464(3) Å), whereas, at 3.355(3) Å, the remaining inner nitrogen is too remote to be considered as bonding to the $\mathrm{Cu^{II}}$ centre. The bipy NCCN torsion angle of 31(1)° is severely reduced from that observed in either the free ligand or the mononuclear complex $[\mathrm{Cu(L)Cl}]^+$. This reduction is required for the bipy unit to chelate the $\mathrm{Cu^{II}}$ ion, and it is clearly too great for both of the "inner" aza nitrogen atoms to be able to complex the other $\mathrm{Cu^{II}}$ ion at the same time; at least one of them is constrained so that its hydrogen is directed towards the metal, hindering any potential Cu–N interaction.

We have applied the extended site-binding model[10] to estimate the degree to which the binding of a first Cu^{II} ion by L affects its affinity for a second Cu^{II} ion. This approach allows the cumulative formation constants for equilibria (1)–(4) to be modelled by one or more microscopic interaction parameters and a statistical factor (ω). The latter (ω) can be computed using a well-established procedure[11] based on the symmetries of the participating species (see the Supporting Information). Defining 1) f^{Cu}_{aza} and f^{Cu}_{bipy} as the microscopic affinities of Cu^{II} for the aza-crown and bipy sites, respectively, and 2) a Boltzmann factor $u^{LL} = e^{-\Delta E^{LL}/RT}$ as the inter-ligand interaction between the two coordinating bipy units (in, for example, $[Cu(L)_2]^{2+}$ and $[Cu_3(L)_2]^{6+}$), we can express the cumulative formation constants of $[Cu(L)_2]^{2+}$ and $[Cu(L)]^{2+}$ as the following:

$$\beta^{Cu,L}_{1,2} = \omega^{Cu,L}_{1,2} \cdot \left(f^{Cu}_{bipy}\right)^2 \cdot u^{LL} \tag{5}$$

$$\beta^{Cu,L}_{1,1} = \omega^{Cu,L}_{1,1} \cdot \left(f^{Cu}_{aza}\right) \tag{6}$$

Introduction of a second Boltzmann factor, $u^{CuCu} = e^{-\Delta E^{CuCu}/RT}$, accounting for the energy cost incurred by simultaneous binding of both the bipy and aza-crown sites, likewise allows us to write the following Equations (7) and (8):

$$\beta^{Cu,L}_{3,2} = \omega^{Cu,L}_{3,2} \cdot \left(f^{Cu}_{bipy}\right)^2 \cdot \left(u^{LL}\right) \cdot \left(f^{Cu}_{aza}\right)^2 \cdot \left(u^{CuCu}\right)^2 \tag{7}$$

$$\beta^{Cu,L}_{2,1} = \omega^{Cu,L}_{2,1} \cdot \left(f^{Cu}_{bipy}\right) \cdot \left(f^{Cu}_{aza}\right) \cdot \left(u^{CuCu}\right) \tag{8}$$

for $[Cu_3(L)_2]^{6+}$ and $[Cu_2(L)]^{4+}$, respectively. Converting Equations (5), (6), (7) and (8) into their logarithmic forms then gives four simultaneous equations from which we calculate the following values (see the Supporting Information for full details):

$$\log\left(f^{Cu}_{bipy}\right) = 7.8 \tag{9}$$

$$\log\left(f^{Cu}_{aza}\right) = 10.3 \tag{10}$$

$$\log\left(u^{LL}\right) = 0.02 \tag{11}$$

$$\log\left(u^{CuCu}\right) = -3.7 \tag{12}$$

Subsequent conversion into absolute energies gives the following final values:

$$\Delta g^{Cu,bipy} = RT\ln\left(f^{Cu}_{bipy}\right) = -44.9\,\mathrm{kJmol^{-1}} \tag{13}$$

$$\Delta g^{Cu,bipy} = RT\ln\left(f^{Cu}_{aza}\right) = -59.3\,\mathrm{kJmol^{-1}} \tag{14}$$

$$\Delta E^{L,L} = RT\ln\left(u^{LL}\right) = -0.1\,\mathrm{kJmol^{-1}} \tag{15}$$

$$\Delta E^{CuCu} = RT\ln\left(u^{CuCu}\right) = +21.6\,\mathrm{kJmol^{-1}} \tag{16}$$

The term u^{CuCu}, from which the intermetallic interaction value of $\Delta E^{CuCu} = +21.6\,\mathrm{kJmol^{-1}}$ is derived, equates to Ercolani's allosteric cooperativity index α.[12] This parameter is typically expressed as the ratio of the (statistically corrected) experimental formation constant of a given multi-component assembly to its equivalent hypothetical (non-cooperative) one. The value of α will be greater than 1 in the case of positive cooperativity and less than 1 in the case of negative cooperativity.[12] In the present case the value of α is given by Equation (17):

$$\alpha = \left(\beta^{Cu,L}_{2,1}/\omega^{Cu,L}_{2,1}\right)/\left(f^{Cu}_{bipy} \cdot f^{Cu}_{aza}\right) = 10^{-3.7}\ (\ll 1) \tag{17}$$

which indicates that severe negative cooperativity accompanies the successive binding of two Cu^{II} ions to the ditopic receptor L. Although electrostatic repulsion between the entering cations cannot be ruled out as a possible source of this energy cost, such effects are known to be largely compensated for by favourable solvation changes associated with the increase in total charge when polymetallic receptors undergo a sequential increase in nuclearity.[13] It is more probable, therefore, that the repulsive interaction has a structural basis: as seen in the solid state, when the bipy unit acts as a bidentate chelate the resulting planarity forces the two "inner" nitrogen atoms at the 3,3′-positions to approach one another, causing one to be an axially elongated donor and outright preventing the other from coordinating Cu^{II} at all. The corresponding energy cost of $\Delta E^{CuCu} = +21.6\,\mathrm{kJmol^{-1}}$ thus reflects the entropic and enthalpic losses associated with the aza-crown being able to coordinate through only three of its nitrogen atoms when the bipy site is bound to a Cu^{II} ion. This applies irrespective of the order in which the two sites are occupied: The structural rearrangements caused by secondary binding of Cu^{II} to the bipy site will require one of the $Cu-N_{aza}$ bonds to break. Alternatively, if the bipy unit is considered as the primary binding site, the aza-crown is already locked in a conformation that prevents it from binding a second Cu^{II} ion through all four N-donors.

In conclusion, we have presented structural and thermodynamic evidence to show how the binding mode and affinity of a ditopic aza-crown/bipy ligand can be influenced by allosteric interactions. The results provide an interesting insight into the mechanism of site interaction in artificial allosteric systems: the two sites are mechanically coupled through conformational restraints. Possible applications for regulating the catalytic activity in for example, dioxygen activation and phosphodiester cleavage reactions are currently being explored.

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Keywords: allosterism · aza-crown compounds · cooperative effects · copper · N ligands

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[4] Crystal data for $C_{16}H_{22}N_6$; $0.6\times0.6\times0.6$ mm; $M_r=298.40$, Monoclinic, $P2_1/n$, $a=9.0171(8)$, $b=10.4120(9)$, $c=16.4432(15)$ Å; $\beta=92.592(2)°$; $V=1542.2(2)$ Å^3; $Z=4$; $Z'=1$; $\rho_c=1.285$ Mg m^{-3}; $F(000)=640$; $\mu(\text{Mo}_{K\alpha})=0.082$ mm^{-1}; $T=100$ K; $\lambda(\text{Mo}_{K\alpha})=0.71073$ Å; 15305 measured reflections; 3806 unique reflections ($R_{int}=0.0284$). The structure was refined on F^2 to $R_w=0.0986$; $R=0.0384$ (3806 reflections with $I>2\sigma(I)$) and GOF = 0.771 on F^2 for 287 refined parameters. Largest difference peak and hole 0.350 and −0.207 e Å^{-3}. CCDC 710578 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[8] Crystal data for $Cu_2C_{16}H_{22}N_6Cl_2\cdot MeCN\cdot 0.5\,MeCO_2Et$; $0.2\times0.075\times0.05$ mm; $M_r=517.94$, Monoclinic; $C2/c$; $a=18.9791(5)$, $b=15.7030(4)$, $c=16.1009(5)$ Å; $\beta=103.9230(10)°$; $V=4657.6(2)$ Å^3; $Z=8$; $Z'=1$; $\rho_c=1.360$ Mg m^{-3}; $F(000)=1976$; $\mu(\text{Cu}_{K\alpha})=3.595$ mm^{-1}; $T=100$ K; $\lambda(\text{Cu}_{K\alpha})=1.54178$ Å; 17740 measured reflections; 4348 unique reflections ($R_{int}=0.0456$). The structure was refined on F^2 to $R_w=0.1052$; $R=0.0399$ (4348 reflections with $I>2\sigma(I)$) and GOF = 1.061 on F^2 for 242 refined parameters. Largest difference peak and hole 1.383 and −0.805 e Å^{-3}. CCDC 710579 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] Crystal data for $\{Cu_2C_{16}H_{22}N_6Cl_4\cdot 1.5\,MeOH\cdot 0.5\,H_2O\}_2$; $0.18\times0.10\times0.02$ mm; $M_r=1246.68$; Monoclinic; $C2/c$; $a=33.163(4)$, $b=11.0684(16)$, $c=14.2704(18)$ Å; $\beta=102.902(6)°$; $V=5105.9(12)$ Å^3; $Z=4$, $Z'=0.5$; $\rho_c=1.622$ Mg m^{-3}; $F(000)=2536$; $\mu(\text{Mo}_{K\alpha})=2.111$ mm^{-1}; $T=150$ K; $\lambda(\text{Mo}_{K\alpha})=0.71073$ Å; 20143 measured reflections. The crystal was pseudo-merohedrally twinned by rotation about the crystallographic *c*-axis (twin law: −1 0 −1, 0 −1 0, 0 0 1); reflections were therefore not merged. The structure was refined on F^2 to $R_w=0.1538$; $R=0.0600$ (20151 reflections with $I>2\sigma(I)$) and GOF = 1.080 on F^2 for 301 refined parameters and 2 restraints. Largest difference peak and hole 1.965 and −0.499 e Å^{-3}. The refined fractional occupancy of the minor crystal domain converged to 0.08313(84). CCDC 710580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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