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The Assembly of "S_3N" – Ligands Decorated with an Azo-Dye as Potential Sensors for Heavy Metal Ions†

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An "S_3N-ligand azo-dye" conjugate has been synthesised with a view to the development of a sensor for heavy metal ions. Complexation of this system with Ag(I), Hg(II) and Cu(II) salts has been investigated and an X-ray structure obtained for a Hg(II) complex. Complexation of the conjugated dye to these metals results in a bathochromic shift in the absorption maximum of the azo dye, an effect which is most pronounced for Cu(II).

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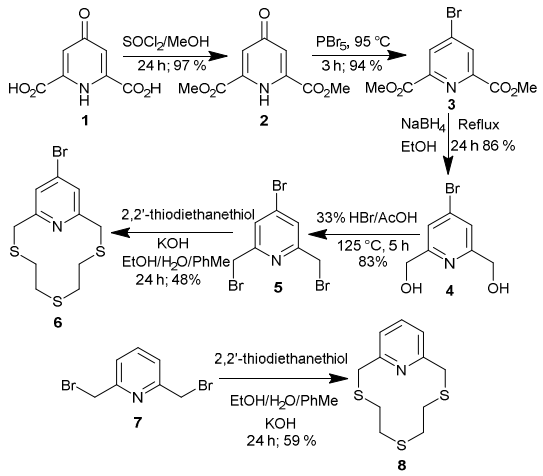
Introduction

In recent years the synthesis and co-ordination chemistry of mixed-donor ligand systems, especially those which contain both hard and soft donor sets, has attracted considerable attention.[1a-l] Recently we reported a general method for the synthesis of mixed hard-soft donor macrocycles[1m] and their subsequent conjugation[2a] with a representative dye with the ultimate aim of developing metal-responsive sensors which are capable of active transport to specific organelles in biological systems.[2b,c] As a continuation of these studies we wished to develop a robust route to the synthesis of macrocyclic pyridine-containg azo-dyes with a view to establishing whether such systems would ligate soft metal ions with a concomitant change in their absorption spectra.[3] This construct would then be incorporated into a sensor for the detection of specific metal ions of biological interest.[4] Our initial studies focussed on the synthesis of derivatives of **8**, an "S_3N" tetradentate ligand[5a] which is known to bind to heavy metal ions.[5] In practice we elected to prepare **6** which was viewed as a key intermediate for the synthesis of a variety of peripherally functionalised macrocyles as exemplified by the dye-crown conjugate **13**.

Results and discussion

The synthesis of **6** was readily accomplished using the methodology developed by Vögtle.[5a] Reaction of 4-bromo-2,6-bis(bromomethyl)pyridine[6], which itself was readily accessible from chelidamic acid,[7] with commercially available 2,2-thiodiethanethiol in the pressence of KOH as base, in a ternary solvent system (aqueous ethanol-toluene), cleanly afforded the desired thia-crown **6**, a colourless crystalline solid, in 48% yield. Macrocycle **8** was similarly prepared, and in a marginally better yield of 59%, from the di-bromide **7** as reported previously.[5a] The structure of the crown **6** was confirmed spectroscopically and also by way of a single crystal X-ray analysis.



Scheme 1. Synthesis of S_3N ligands

The X-ray structure of **6** (**Figure 1**) proved to be similar to that previously reported[5b] for **8** in that torsion angles about the -S-C-C-S moiety are all close to 180°, presumably in an order to maximise lone pair-lone pair repulsion.[8]

At this stage we wished to investigate an appropriate method for the conjugation of a "reporter" dye unit with the pyridine ring of the macrocycle, of which one of the plethora of palladium-catalysed coupling reactions (*e.g.* Heck or Stille reaction) appeared to be most convenient. After some investigation we concluded that the most efficient approach to this coupling reaction, leading to **13**, was *via* a Suzuki reaction between an appropriate boronate ester such as **12** and the macrocycle **6** (**Scheme 2**). In the event the key boronate esters **10** and **12** were found to be readily accesible[9] from the palladium catalysed coupling between either **3** and **11** with B_2pin_2, **9** (in 74% and 79% yield respectively).

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† Electronic Supplementary Information (ESI) available: [full experimental procedures for the preparation of all new compounds]; crystallographic data [CCDC deposition nos. 1445157-1445161, 1445149 and 1445150] are available from www.ccdc.cam.ac.uk. See DOI: 10.1039/x0xx00000x.

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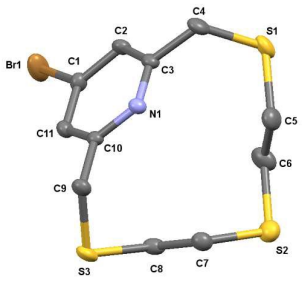
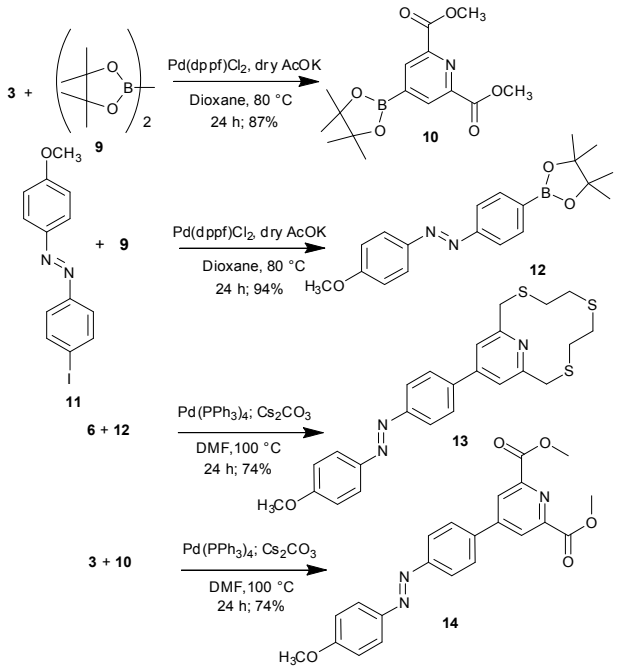


Figure 1: X-ray crystal structure of macrocycle **6** (Ellipsoids at 50% probability level. Selected bond lengths and torsion angles are to be found in the ESI).

Gratifyingly the Suzuki[10] reactions between **6** and **12** and **3** with **10** also proceeded in acceptable yields, affording the desired thiocrown-azo dye hybrid **13** and di-ester **14** in yields of 57% and 53% respectively. Both **13** and **14** were obtained as crystalline solids whose structures were confirmed by way of single crystal X-ray diffraction studies (**Figure 2**). The X-ray structure of **13** again revealed that the macrocycle adopts a conformation in which the torsion angles about the S-C-C-S- motif are close to 180°, presumably in order to minimise lone pair-lone pair repulsions.[8, 11a] All of ther sulfur atoms are *exo*-disposed[11a,b] with respect to the macrocycle while the pyridine moiety is orientated such that the nitrogen lone pair is axial with respect to the plane containing the macrocyclic core.

Having developed a route to the requisite azo-dyes **13** and **14** we have briefly investigated their complexation with representative, "soft" metal ions including silver (I), copper (II) and mercury (II). The metal complexes of the macrocycles **6**, **8** and di-ester **14** were also investigated for comparison purposes. Hence, reaction of each of the ligands **6, 8** and **13** with one molar equivalent of silver nitrate in methanolic dichloromethane (1:1) afforded the silver complexes **15-17**. The formation of complexes **15-17** was inferred from analytical data and by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of complexes **15-17** in DMSO-d_6 (**Figure 4**) were characterised by a downfield shift of the benzylic, methylene protons, H1, ($\Delta\delta$ ca. 0.3 ppm in each case) when compared to the resonances of these hydrogens in the free ligands, an observation which is in keeping with literature precedent.[5a] In addition, complex formation also resulted in the splitting of the $H_{2,3}$-methylene protons, originally observed as a broadened singlet at ca. δ 2.5 ppm in the free ligand, into two broadened multiplets which appeared between δ 2.5-2.8 ppm, as illustrated in **Figure 4**.



Scheme 2. Suzuki reaction leading to functionalised azo-dyes.

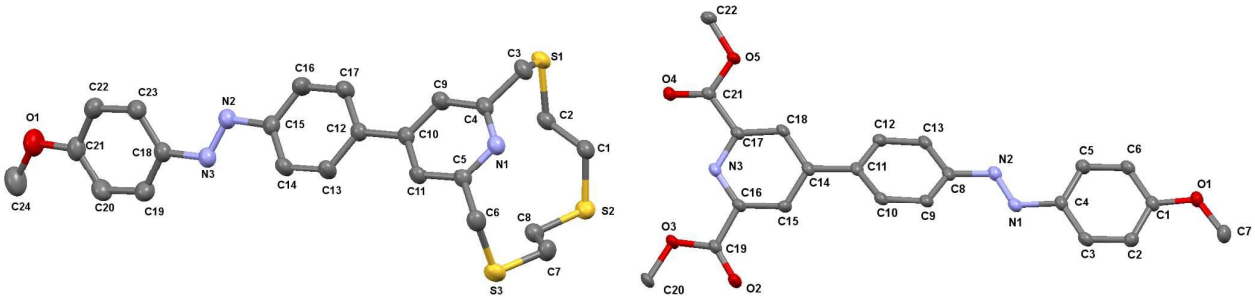


Figure 2: X-ray crystal structures of ligand **13** and azo-dye **14** (Ellipsoids at 50% probability level. Selected bond lengths and torsion angles are to be found in the ESI).

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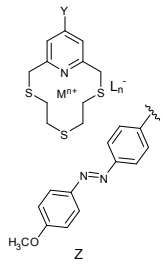

Complex	Y	M_n^+	L_n^-
15	H	Ag(I)	NO_3^-
16	Br	Ag(I)	NO_3^-
17	Z	Ag(I)	NO_3^-
18	H	Cu(II)	NO_3^-
19	Br	Cu(II)	NO_3^-
20	Z	Cu(II)	NO_3^-
21	H	Hg(II)	Cl^-
22	Br	Hg(II)	I^-
23	Z	Hg(II)	I^-

Table 1. Complexes prepared in this study.

Ligation of **6, 8** and **13** to silver is also associated with changes to the aromatic region of their ^{1}H NMR spectra (**Figure 4**). The changes noted in the ^{1}H NMR spectrum of the azo-dye **13** upon complexation with Ag^+ are also similar to those observed when the ^{1}H NMR spectrum of **13** was conducted in the presence of TFA in CD_2Cl_2. This observation implies that, in the case of **13** at least, the pyridine nitrogen is co-ordinated to silver during complexation (Figure 3). Unfortunately, although the available spectroscopic data is also indicative of an association of the Ag^+ ion with ligands **6, 8** we were not able to grow crystals crystals of sufficient quality to obtain their X-ray structures.

Reaction of Cu(II)nitrate trihydrate with ligand **6** afforded the green-coloured complex **19** which yielded crystals of crystallographic quality upon slow recrystallisation from CH_2Cl_2-MeOH. The X-ray structure of **19** (**Figure 3**) showed the copper to be in a distorted octahedral environment with the three sulphur atoms of the ligand being equatorially disposed. The remaining equatorial co-ordination site was occupied by a η^1-nitrato ligand while the remaining axial co-ordination sites were occupied by the pyridyl nitrogen of the macrocycle and a molecule of water.[12] sulphur atoms of the ligand equatorially disposed. Charge neutrality in this case is maintained by an additional nitrate anion which does not appear to be bound directly to the copper centre. The observed Cu(1)-N(1) bond length of 1.978(3) Å was considerably shorter than those of the Cu-S bonds (Cu-S(1), Cu(1)-S(3), Cu(1)-S(2) is 2.3736(9) Å, 2.4301(8) Å, 2.7304(10) Å) and the Cu(1)-O(2) bond with the nitrate ligand (2.335(3) Å).

Similarly, complexation of **6**, **8** and **13** with either Hg_2Cl_4 or Hg_2I_4 in MeOH-CH_2Cl_2 afforded the crystalline complexes **21**, **22** and **23** whose solid state structures were also determined by single crystal X-ray crystallography (**Figures 5 and 6**). All three of these complexes were found to contain mercury in two very different co-ordination environments. In the case of **21**, **22** and **23**, one of the Hg^{2+} cations is bound, in an *endo*cyclic manner, to the three sulphur atoms and the pyridine nitrogen atom of the macrocyclic core; these *endo*-bound Hg^{2+} centres adopt highly distorted square pyramidal co-ordination geometries in each case (τ 0.05, 0.31 and 0.37 respectively).[13] The remaining apical co-ordination site is, in each case, occupied by a halide ligand (either Cl^- or I^-). The large Hg^{2+} cation lies above the mean plane of the "S_3N" cavity. Overall charge neutrality in these complexes is now maintained by the presence of halide-bridged dimer, $[Hg_2X_6]^{2-}$, in which mercury adopts highly distorted tetrahedral geometries (see ESI for details). The X-ray structures of these complexes are similar to that previously reported[5d] for **8**·2($HgCl_2$) except that, in the latter case, the structure is best represented as [**8**-HgCl]$^+$ and $[HgCl_3]^-$ in which the counter anion adopts a trigonal planar co-ordination geometry which is weakly bound to the macrocycle-bound mercury centre. The binding of Hg^{2+} to the macrocyclic core of **13** is also inferred from ^{1}H NMR data where the benzylic protons in the Hg^{2+} complex experience line broadening and a slight downfield shift ($\Delta\delta$ of *ca.* 0.03 ppm) when compared to the those in the free ligand.

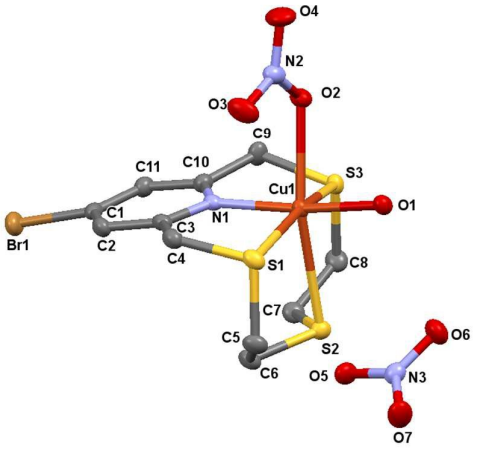

Figure 3: X-ray **c**rystal structure of **19** (Ellipsoids at 50% probability level. Selected bond lengths and torsion angles are to be found in the ESI).

Examination the X-ray structure of the macrocycle-dye conjugate **13** also reveals that while the central aryl and pyridine rings are almost co-planar (C(9)-C(10)-C(12)-C(17) = -8.3(3)°; C(11)-C(10)-C(12)-C(13) = -9.3(3)°) there is considerable deviation from co-planarity about the central aromatic ring and the azo moiety (C(16)-C(15)-N(2)-N(3) = 162.9(2)°; C(14)-C(15)-N(2)-N(3) = -18.6(3)°). The azo-link is *E*-configured (C(15)-N(2)-N(3)-C(18) = 178.35(16)°).

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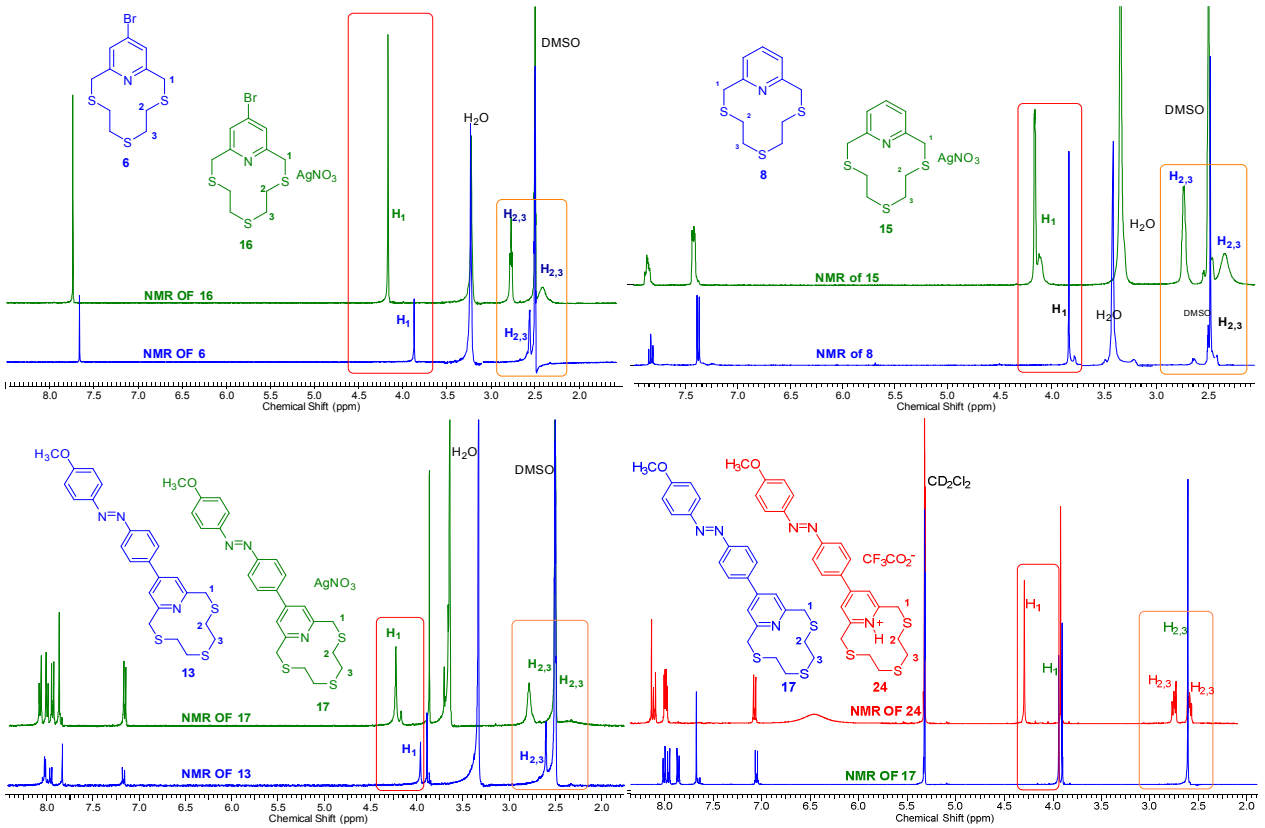
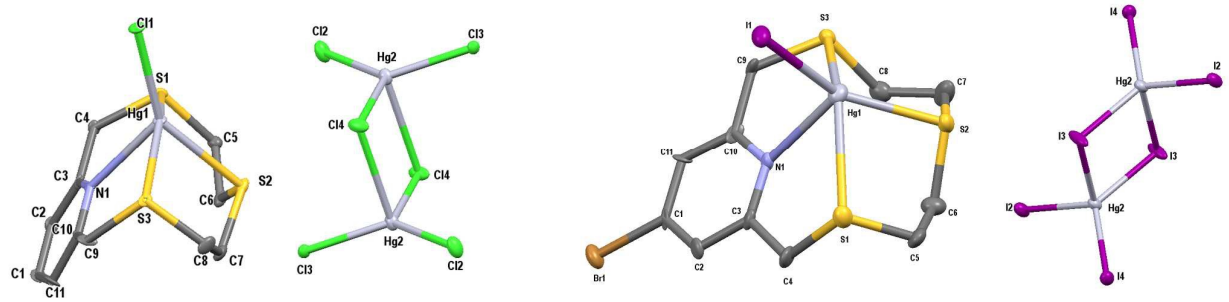


Figure 4: ^{1}H NMR spectra of the free ligands **6**, **8** and **13** together and their spectra when determined in the presence of Ag^+ and TFA.



Complex 21 **Complex 22**

Figure 5: X-ray crystal structure of complexes **21** and **22** (Ellipsoids at 50% probability level. Selected bond lengths and torsion angles are to be found in the ESI).

These values are somewhat attenuated (**Figure 6**) upon complexation with Hg_2I_4 (C(14)-C(15)-N(2)-N(3) = 154.4(9)° and C(16)-C(15)-N(2)- N(3) = -27.2(13)° while maintaining an *E*-configured azo-moiety (C(15)-N(2)-N(3)-C(18) = 177.7(8)°), observations which are similar to those reported for related push-pull azo-dyes and their complexes.[3c] Complexation of

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Hg^{2+} by **13** also induces a conformational change in the 1,4,7-10-azacyclododecane core. For example, in the free ligand, **13**, the torsion angles about S(1)-C(3)-C(4)-N(1) and N(1)-C(5)-C(6)-S(3) are 118.67(17)° and -98.68(18)° respectively. These parameters change dramatically upon complexation such that in the Hg^{2+} complex, **23**, the torsion angles for S(3)-C(9)-C(10)-N(1) becomes -21.8(11)° and that for N(1)-C(3)-C(4)-S(1) becomes -15.0(11)° respectively, an outcome which is similar to that reported for the complex of **8** with $HgCl_2$.[5d]

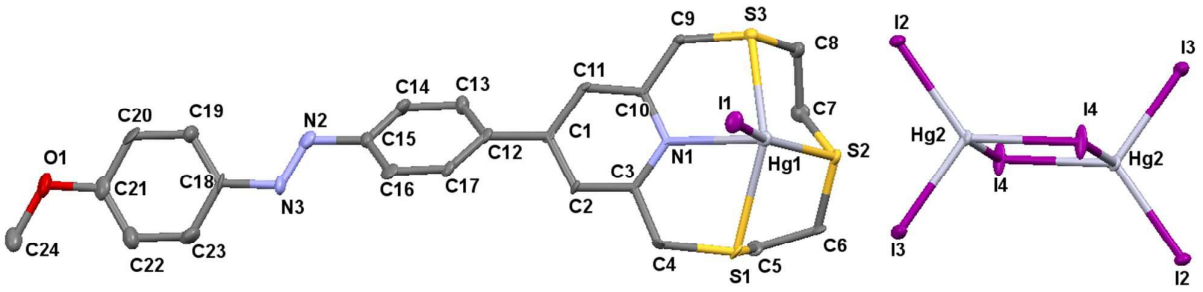

Figure 6: X-ray structure of complex **23** (Ellipsoids at 50% probability level. Selected bond lengths and torsion angles are to be found in the ESI).

The UV-visible spectra of **17**, **20** and **23** in ethanol, which appear yellow-orange in colour, all display small bathochromic shifts[3i] when reacted with 1 equivalent of a selection of metal salts (1 mg/50 mL of ethanol) [Ag complex: λ_{max} = 364 nm(ε = 4.5 x 10^5), Cu complex λ_{max} = 372 nm(ε = 4.3 x 10^5) and Hg-complex is λ_{max} = 364 nm(ε = 5.3 x 10^5)] with respect to the uncomplexed ligand **13** [λ_{max} 358 nm (ε = 4.0 x 10^5)]. A small bathochromic shift is also observed when the UV spectrum of **13** is conducted in the presence of TFA, generating trifluoroacetate salt **24** (1 mg of **13**/50 mL of ethanol; 0.01 mL of TFA; λ_{max} 363 nm (ε = 4.4 x 10^5)), **Figure 7**.

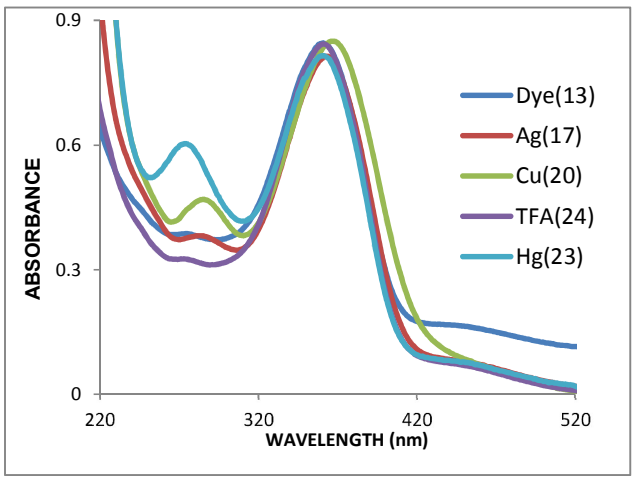

Figure 7: UV studies of dye **13** and its complexes **17**, **20**, **23** and salt **24** in ethanol solution (1 mg/ 50 mL of ethanol at 20 °C).

DFT Calculations

We have undertaken DFT studies at the B3LYP[14]/Def2-TZVP[15a] level in order to gain information as to the structure and bonding of these ligands and complexes and also to probe the factors responsible for the absorption spectra of **13**, **20** and **23**. All calculations were performed using the Gaussian suite of programs.[16]

In the optimised (gas phase) structure of **13** we find that the two rings joined by the diazo unit are strongly coplanar with dihedral angle, C(16)-C(15)-N(2)-N(3) = -179.2°, in contrast to the crystal structure (162.9°). For the two rings on the same side of the diazo unit we find the computed dihedral angles to be larger, e.g. C(9)-C(10)-C(12)-C(17) = -35.5°, compared with the crystal structure (-8.3°). Other key angles are compared in **Table 2**.

The computed absorption bands of **13**, **20** and **23** corresponding to the bands shown in figure 7 are listed in **Table 3** with the associated oscillator strength and the weights of the principal excitations involved. The B3LYP functional used in this work is known to underestimate the transition energies associated with charge transfer bands. However our concern here is for a relative comparison of the nature of the bands and for this analysis the B3LYP functional is adequate. We find that in **13**, the band shown is not dominated by a HOMO → LUMO transition but rather the HOMO-1 → LUMO transition. The band corresponding to the HOMO → LUMO transition is found 31 nm lower in wavelength with a relatively small oscillator strength (0.075 versus 1.232). The relevant orbitals are depicted in **Figure 8(a)** and show that the transition corresponds to transfer of charge from the terminal, electron rich, ring attached to the azo unit towards the electron deficient, macrocycle, end. The orbitals on the azo moiety change from bonding to antibonding in this transition. In **23**, λ_{max} does correspond to the HOMO → LUMO transition and shows a stronger charge transfer from the terminal, electron rich, ring towards the pyridine ring which is bond to the metal, see **Figure 8(b)**. For **20**, a similar picture emerges (**Figure 8(c)**) but the effect is less marked than in **23**.

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Angles/°	13	23	20
C(9)-C(10)-C(12)-C(17)	-35.5	28.8	31.9
C(11)-C(10)-C(12)-C(13)	-35.6	29.5	32.0
C(16)-C(15)-N(2)-N(3)	-179.2	179.4	-175.4
C(14)-C(15)-N(2)-N(3)	0.9	-0.9	4.8
N(2)-N(3)-C(18)	116.0	116.3	116.3

Table 2. Key angles in computed structures (B3LYP/Def2-TZVP).

Molecule	λ_{max} / nm	Oscillator Strength	Principal Transitions	Weights of Transitions
13	378	1.232	HOMO-1 → LUMO HOMO-2 → LUMO	0.395 0.096
23	353	0.599	HOMO → LUMO+3	0.370
20	347	0.416	$(HOMO)_\alpha \rightarrow (LUMO)_\alpha$	0.364

Table 3. λ_{max} absorption bands, oscillator strength and the weights of the principal excitations (B3LYP/Def2-TZVP).

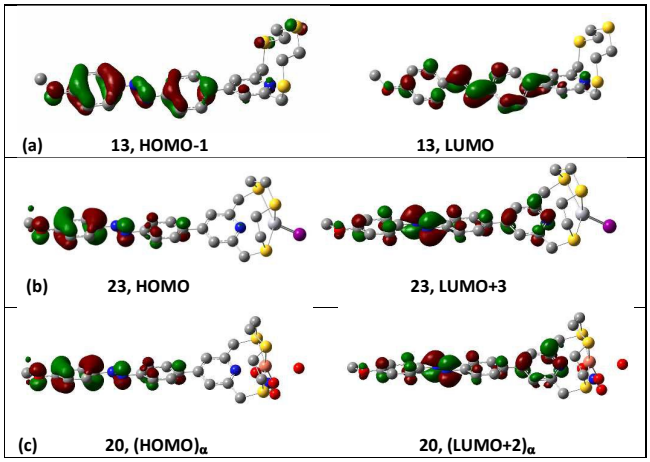

Figure 8. MO orbitals associated with λ_{max} for **13**, **20** and **23**.

Experimental

General Experimental details

Synthetic procedures were carried out under an atmosphere of nitrogen in dry solvents unless stated otherwise. All reagents and solvents were reagent grade and were used without further purification. Chromatographic purifications were performed using silica gel SDS (particle size 0.04-0.06 mm). A Sanyo Gallenkamp melting point apparatus was used for melting point determinations; these values are uncorrected. Infrared spectra were measured using a Bruker Alpha ATR FT-IR instument as evaporated films; absorption peaks ($\tilde{\nu}_{max}$) are quoted in wave numbers (cm^{-1}). Deuterated chloroform ($CDCl_3$) was used as solvent unless otherwise stated to record Nuclear magnetic resonance (NMR) spectra. ^{1}H NMR spectra were recorded on Bruker Advance Ultra shield 300 (300 MHz), Bruker Advance Ultrashield 500 (500 MHz). Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m). Low resolution mass spectra were measured on Micromass Trio 200 spectrometer. High resolution mass spectra were measured on Kratos Concept IS spectrometer. A Carlo Erba EA 1108 Elemental Analyzer was used for determination of % levels of carbon, hydrogen and nitrogen. A Metrohm 686 Titroprocessor +665 Dosimat Autotitor was used to measure chlorine content.

Synthesis of 1,4-Dihydro-4-oxo-2,6-pyridinedicarboxylic acid, 1.[17]

The first part of this preparation involved the synthesis of 4-oxo-4*H*-pyran-2,6-dicarboxylic acid (chelidonic acid)[14b]: a solution of sodium ethoxide was prepared by dissolving sodium (2.4 g, 0.1 mol) in 36 mL of anhydrous ethanol. To this mixture was added a mixture of dry acetone (4 mL, 0.05 mmol) and diethyl oxalate (14.5 g, 0.11 mol). During the addition of two mixtures a yellow precipitate formed. The reaction was stirred for an hour at 60 °C to complete the reaction, then 20 mL of 37% of HCl and 10 mL of water was added and it was left to stir for one day at 50 °C. Excess ethanol was removed under reduced pressure, and then 30 mL of water and 5 mL of HCl was added and was left to stir at ambient temperature for a further period of 3 – 4 days. The crude product which had been deposited was collected by filtration at the pump, washed (water and then ice-cold acetone) to afford 4-oxo-4*H*-pyran-2,6-dicarboxylic acid (chelidonic acid) as a brown-coloured, amorphous, solid. Yield 11.54 g (42%); mp 247 – 248 °C (lit[17b]: 157 °C). ^{1}H NMR: (methanol-d_4, 300 MHz) δ ppm 7.01 (2H, s, ArH). ^{13}C NMR: (methanol-d_4, 75 MHz) δ ppm 119.96, 156.97, 162.44, 182.84. $\tilde{\nu}_{max}$ (ATR): 1229, 1583, 1633, 1742, 2560, 3078 cm^{-1}. MS (ES^+): *m/z* $[M+H]^+$ 185; $[M+Na]^+$ 207. Accurate Mass (ES^+): $[C_7H_4O_6]^+$ requires 184.0008 found 184.0021.

Aqueous ammonia (80 mL of a 35% aqueous solution) was added drop-wise to chelidonic acid (7.91 g, 42.9 mmol) at 0 °C. Upon completion of the addition the reaction mixture was stirred for two days at room temperature. Excess ammonia was removed under reduced pressure and the solid was brought to reflux with 80 mL of water and 1.6 g of charcoal for 5 minutes. The mixture was filtered through celite® and the filtrate allowed to cool to ambient temperature. The filtrate was then acidified to pH 1 by the careful addition of 37 % aqueous HCl which resulted in the precipitation of the crude product, a colourless crystalline solid. The *title compound* was collected at the pump and washed with ice-cold water (3 x 30 mL) and dried *in vacuo*. Yield 5.53 g (70%); mp 254 - 255 °C, lit.[17]: 248 °C). ^{1}H NMR: (methanol-d_4, 300 MHz) δ ppm 6.95 (2H, s, ArH). ^{13}C NMR: (methanol-d_4, 75 MHz) δ ppm 117.3, 145.3, 165.9, 184.4. $\tilde{\nu}_{max}$ (ATR): 1336, 1392, 1460, 1609, 1710, 2498, 3120, 3446, 3605 cm^{-}. MS (ES^+): *m/z* $[M+H]^+$ 183; $[M+Na]^+$ 205. Accurate Mass (ES^+): $[C_7H_6NO_5]^+$ requires 184.0246; found 184.0241.

Synthesis of dimethyl 4-oxo-2,6-1,4-dihydropyridine-2,6-dicarboxylate, 2.[18]

Thionyl chloride (22.3 mL, 306 mmol, 8 eq) was added dropwise to methanol (70 mL) which was cooled to -10 °C. Chelidamic acid (7 g, 38.2 mmol) was also added to the mixture. The solution was left to stir for 24 hours at room temperature and then heated at reflux for an additional 2 hours. The excess of thionyl chloride and the solvent was

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removed under reduce pressure to give the *title compound* as a colourless, crystalline solid. Yield 7.85 g (97%); mp 162 - 165 °C (lit.[18]: 169 – 170 °C). ^{1}H NMR: (methanol-d_4, 300 MHz) δ ppm 3.99 (6H, s, CH_3), 7.78 (2H, s, ArH). ^{13}C NMR: (methanol-d_4, 300 MHz) δ ppm 54.8, 117.7, 145.6, 161.6, 174.7. $\tilde{\nu}_{max}$ (ATR): 1187, 1348, 1478, 1558, 1724, 3106 , 3307 cm^{-1}. MS (ES$^+$): *m/z* $[M+H]^+$ 212; $[M+Na]^+$ 234. Accurate Mass (ES$^+$): $[C_9H_{10}NO_5]^+$ requires 212.0552; found 212.0554.

Synthesis of dimethyl 4-bromopyridine-2,6-dicarboxylate, 3.[19]

A mixture of dimethyl 4-oxo-2,6-1,4-dihydropyridine-2,6-dicarboxylate, **2** (6.6 g, 31.4 mmol) and PBr_5 (27.04 g, 62.8 mmol) were heated together at 90 °C for 3 hours. After this time the reaction mixture was allowed to cool down to room temperature and quenched by the careful addition of hot methanol (15 mL) which resulted in the precipitation of the *title compound*. Collection of the precipitate at the pump and drying *in vacuo* afforded the product, essentially pure by ^{1}H NMR, as a pale beige-coloured amorphous solid. Yield 7.62 g (88%); mp 153 - 156 °C; (lit[19] 155 – 156 °C). ^{1}H NMR: (methanol-d_4, 300 MHz) δ/ppm 4.06 (6H, s, CH_3), 8.49 (2H, s, ArH). ^{13}C NMR: (methanol-d_4, 75 MHz) δ/ppm 53.4, 131.3, 135.1, 149.1, 164.0. $\tilde{\nu}_{max}$ (ATR): 1146, 1246, 1263, 1326, 1442, 1714, 2951, 3077 cm^{-1}. MS (ES$^+$): *m/z* $[M+H]^+$ 273.97. Accurate Mass: $[C_9H_9N_1O_4{}^{80}Br_1]$ requires; 273.9709; found 273.9708. Microanalysis: $C_9H_8BrNO_4$ requires: C, 39.44; H, 2.94; N, 5.11; Br, 29.15 found: C, 39.07; H, 3.09; N, 5.12; Br, 29.07 %.

Synthesis of 4-bromo-2,6-pyridinedimethanol, 4.[20]

Bromo ester **4** (5.0 g, 18.2 mmol) was dissolved in anhydrous EtOH (130 mL) and the mixture cooled to 0 °C. To this suspension was added $NaBH_4$ (3.33 g, 88 mmol) and the mixture stirred at 0 °C for one hour, at room temperature for another hour and at reflux temperature for 1 day. On cooling to ambient temperature acetone (85 mL) was added and the mixture brought to reflux for one hour. The solvent was removed *in vacuo* and the waxy residue was recrystallized from water to afford the *title compound* as an amorphous, colourless, solid. Yield 2.95 g (74%); mp 152 - 156 °C (lit.[20]: 158 – 160 °C). ^{1}H NMR: (DMSO-d_6, 500 MHz) δ ppm 4.53 (4H, s, CH_2), 7.52 (2H, s, ArH). ^{13}C NMR: (methanol-d_4, 75 MHz) δ ppm 63.61 (C4), 121.04 (C2), 133.20 (C1), 163.19 (C3). $\tilde{\nu}_{max}$ (ATR): 1305, 1361, 1403, 1566, 1566, 2763, 3093, 3344 cm^{-1}. Microanalysis: $C_7H_8BrNO_2$ requires: C, 38.56; H, 3.7; N, 6.42 %; found: C, 38.39; H, 3.86; N, 6.13 %.

Synthesis of 4-bromo-2,6-bis(bromomethyl)pyridine, 5.[21]

Diol **4** (2.8 g, 13.1 mmol) and 33% HBr in acetic acid (50 mL) were heated at 125 °C for 5 hours. The reaction mixture was then poured onto ice the pH adjusted to pH 4 – 5 by the addition of 1 M NaOH. At this stage the *title compound* precipitated out of solution as a white powder which was collected at the pump. Yield 3.9 g (89%); mp 127-129 °C (lit.[21]: 125-126 °C). ^{1}H NMR: (400 MHz, DMSO-d_6) δ ppm 4.66 (4H, s, CH_2) 7.81 (2 H, s, Ar-H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 33.5, 125, 133.4, 158.6. $\tilde{\nu}_{max}$ (ATR): 2971, 1563, 1452, 1355, 1283 cm^{-1}. MS (ES$^+$): *m/z* $[M+H]^+$ 341.8; Accurate Mass: $[C_7H_7N^{79}Br_3]^+$ requires: 341.8128; found: 341.8129.

Synthesis of 13-bromo-3,6,9-trithia-15-azabicyclo[9.3.1]pentadeca-1(15),11,13-triene, 6.

To a stirred solution of 4-bromo-2,6-bis(bromomethyl)pyridine (0.791 g, 2.11 mmol), **5** in toluene (25 mL) was added 2,2-thiodiethanethiol (0.28 mL, 2.11 mmol), and a solution of KOH (0.24 g, 4.22 mmol) in ethanol/H_2O 50:1 (25 mL). The bi-phasic reaction mixture was stirred at room temperature for 24 hours after which time the solvent was removed *in vacuo*. The residue was triturated with DCM (50 mL) and the organic extracts washed (6 x 30 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purification of the residue by column chromatography (silica; DCM:Pet 1:1) afforded the *title compound* as a crystalline solid. Yield 0.341 g (48%), mp 122-123 °C. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ/ppm 2.52 (8H, s, H), 3.79 (4H, s,), 7.49 (2H, s,) ^{13}C NMR: ($CDCl_3$, 100 MHz) δ ppm 30.1, 31.0, 35.4, 125.7, 134.6, 158.7. $\tilde{\nu}_{max}$ (ATR): 1187, 1348, 1478, 1558, 1724, 3106, 3307 cm^{-1}. MS (ES$^+$): *m/z* $[M+H]^+$ 336 Accurate Mass (ES+): $[C_{11}H_{14}{}^{79}BrNS_3]^+$ requires 335.9547; found 335.9545. Microanalysis: $C_{11}H_{14}BrNS_3$ requires: C, 39.28; H, 4.2; N, 4.16 %; found: C, 39.16; H, 4.17; N, 3.82 %.

Synthesis of 3,6,9-trithia-1(2,6)-pyridinacyclodecaphane, 8.[5a]

To a stirred solution of 2,6-bis(bromomethyl)pyridine, **7** (0.56 g, 2.11 mmol) in toluene (25 mL) was added 2,2-thiodiethanethiol (0.28 mL, 2.11 mmol), and KOH (0.24 g, 4.22 mmol) dissolved in ethanol/H_2O 50:1 (25 mL). The bi-phasic reaction mixture was then stirred vigorously at room temperature for 24 hours. The solvent was then removed *in vacuo* and the residue dissolved in DCM (100 mL). The organic extracts were washed with water (6 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica; DCM:Pet; 1:1) affording the *title compound* as a colourless, crystalline solid. Yield 0.39 g (72%); mp 164-165 °C (lit.[5a]: 162-163 °C) of pure compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.50 (s, 8H) 3.85 (s, 4H) 7.38 (d, *J* = 8 Hz, 2H) 7.84 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 29.6, 30.5, 35.3, 122.5, 138.8, 157.5. $\tilde{\nu}_{max}$ (ATR): 2921, 1588, 1569, 1451, 1428, 1280, 1208, 1154 cm^{-1}. MS (ES$^+$): *m/z* $[M+H]^+$ 258.2 Accurate Mass (ES+): $[C_{11}H_{15}NS_3]^+$ requires: 257.0361; found: 257.0362.

Synthesis of dimethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2,6-dicarboxylate, 10.[22]

Compound **10** was prepared using an adaption of the procedure reported by Maury *et al.*[22] A mixture of dimethyl 4-bromopyridine-2,6-dicarboxylate, **3** (1.43 g, 5.25 mmol), *bis*(pinacolato)diboron (2.0 g, 8.0 mmol), Pd(dppf)Cl_2 (0.08 g, 0.11 mmol) and dry potassium acetate (1.6 g, 16.0 mmol) in anhydrous 1,4-dioxane (25 mL) was heated at 80 °C for 24 hours. After cooling to room temperature, the reaction mixture was poured into water and then extracted with DCM. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo.* Purification of the residue by column chromatography (silica; hexane:DCM; 2:1) afforded the *title compound* as brown-coloured solid. Yield 1.4 g (87%), mp 116-117 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.37 (12H, s), 4.02 (6H, s), 8.63 (2H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 24.9, 53.1, 83.4, 85.1, 133.1, 147.5, 165.1. $\tilde{\nu}_{max}$ (ATR): 2975, 1710, 1436, 1401, 1339, 1280 cm^{-1}. MS (ES+): m/z $[M + H]^+$ 322.

Synthesis of (*E*)-1-(4-methoxyphenyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)diazene, 12.

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A mixture of (*E*)-1-(4-iodophenyl)-2-(4-methoxyphenyl)diazene,[23] **11** (1.45 g, 5.25 mmol), *bis*(pinacolato)diboron (2.0 g, 8.0 mmol), $Pd(dppf)Cl_2$ (0.08 g, 0.11 mmol) and dry potassium acetate (1.6 g, 16.0 mmol) in anhydrous 1,4-dioxane (25 mL) was heated at 80 °C for 24 hours. After cooling to room temperature, the reaction mixture was poured into water and then extracted with DCM (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* affording the *title compound* as dark red-coloured solid which was essentially pure by ^{1}H NMR analysis. Yield 1.6 g (94%); **mp** 154-155 ˚C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.29 (12H, s), 3.80 (3H, s), 6.93 (2H, d, *J* = 9.5 Hz), 7.78 (2H, d, *J* = 9.0 Hz), 7.83 - 7.88 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 24.5, 55.2, 83.1, 83.6, 113.8, 121.4, 124.5 (**C**$_3$), 135.3, 146.7, 154.1, 161.9. $\tilde{\nu}_{max}$ (ATR): 2993, 1499, 1438, 1353, 1306, 1274, 1209, 1170 cm^{-1}. MS (ES+): m/z $[M+H]^+$ 339.4. Accurate Mass: $C_{19}H_{23}N_2O_3B$ requires 338.1790; found 338.1795.

Synthesis of (*E*)-1-(4-((4-methoxyphenyl)diazenyl)phenyl)-3,6,9-trithia-1(2,6)-pyridinacyclodecaphane, 13.

To a solution of (*E*)-1-(4-methoxyphenyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)diazene, **12** (0.603 g, 1.8 mmol), $Pd(PPh_3)_4$ (205 mg, 0.18 mmol) in DMF (30 mL) was added Cs_2CO_3 (405 mg, 5.4 mmol) and 13-bromo-3,6,9-trithia-15-azabicyclo[9.3.1]pentadeca-1(15),11,13-triene, **6** (0.608 g, 1.8 mmol). The reaction mixture was heated at 110 °C for 24 hours. After this time the reaction mixture was concentrated *in vacuo* and the residue triturated with ethyl acetate (50 mL). The organic extract was washed (with brine and then water), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica; hexane:DCM, 2:1) to afford the *title compound* as an orange-coloured, crystalline, solid. Yield 0.62 g (74%), mp 133-134 ˚C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 2.61 (8H, s), 3.91 (3H, s), 3.94 (4H, s), 7.05 (2H, d, *J* = 8.8 Hz), 7.67 (2H, s), 7.86 (2H, d, *J* = 8.8 Hz), 7.96 (2 H, d, *J* = 9.0 Hz, Ar-H$_7$), 8.01 (2 H, d, *J* = 9.0 Hz, Ar-H$_6$). ^{13}C NMR (125 MHz, CD_2Cl_2) δ ppm 31.1, 31.8, 32.5, 55.7, 114.7, 123.6, 124.1, 125.6, 129.3, 135.3, 147.2, 154.5, 155.2, 158.3, 163.1. $\tilde{\nu}_{max}$ (ATR): 2962, 1581, 1453, 1420, 1393, 1248, 1193 cm^{-1}. MS (ES$^-$): *m/z* $[M-H]^-$ 466.7; $[M + H]^+$ 468.2. Accurate Mass: $C_{24}H_{26}N_3O_1S_3$ requires 468.1233 found 468.1230.

Synthesis of dimethyl (*E*)-4-(4-((4-methoxyphenyl)diazenyl)phenyl)pyridine-2,6-dicarboxylate 14. To a solution of (*E*)-1-(4-methoxyphenyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)diazene, **12** (0.603 g, 1.8 mmol), $Pd(PPh_3)_4$ (205 mg, 0.18 mmol) in DMF (30 mL) was added Cs_2CO_3 (405 mg, 5.4 mmol) and dimethyl 4-bromopyridine-2,6-dicarboxylate, **3** (0.491 g, 1.8 mmol). The reaction mixture was heated at 110 °C for 24 hours. After this the reaction mixture was reduced *in vacuo* and the residue triturated with ethyl acetate. The organic extracts were washed (brine and then water), dried ($MgSO_4$) and reduced *in vacuo*. The residue was purified by column chromatography (silica; hexane:DCM, 2:1) affording the *title compound* as orange powder. Yield 0.54 g (74%), mp 141-142 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.92 (3H, s), 4.08 (6H, s), 7.05 (2H, dd, *J* = 8.8, 2.2 Hz), 7.92 (2H, dd, *J* = 8.0, 1.7 Hz), 7.98 (2H, dd, *J* = 8.8, 2.5 Hz), 8.05 (2H, dd, *J* = 8.0, 1.5 Hz), 8.62 (2H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 53.3, 55.6, 114.3, 123.5, 125.1, 125.6, 127.9, 137.5, 147.0, 148.9, 150.3, 150.6, 162.6, 165.2. $\tilde{\nu}_{max}$ (ATR): 2959, 1499, 1412, 1349, 1313, 1294, 1195 cm^{-1}. MS (ES$^-$): m/z $[M+H]^+$ 406.2. Accurate Mass: $C_{22}H_{20}N_3O_5$ requires 406.1411; found 406.1416.

Metal complexation studies:

Synthesis of silver(I) complex (15).[5a,24]

A solution of silver nitrate (0.02 g, 0.1 mmol) in methanol (8 mL) was added slowly, over a period of 20-25 minutes at room temperature, to a solution of 3,6,9-trithia-1(2,6)-pyridinacyclodecaphane, **8** (0.03 g, 0.1 mmol) in DCM (8 mL). Slow evaporation of the reaction mixture at ambient temperature afforded the *title compound* as a colourless powder. Yield 0.038 g (89%), mp 219-220 °C (lit.[5a]: 217-219 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (4H, d, *J* = 4 Hz), 3.16 (4H, br. s.) 4.16 (4H, d, *J* = 3.0 Hz), 7.42 (2H, dd, *J* = 8, 3 Hz), 7.87 (1H, td, *J* = 8, 3.5 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 30.1, 31.3, 37.2, 124.4, 138.7, 156.1. $\tilde{\nu}_{max}$ (ATR): 3055, 2949, 1471, 1386, 1359, 1343 cm^{-1}. MS (ES^+): m/z $[M+H]^+$ 428.4.

Synthesis of silver(I) complex, 16.

A solution of silver nitrate (0.008 g, 0.05 mmol) in methanol (4 mL) was added slowly, over a period of 20-25 minutes at room temperature, to a solution of 13-bromo-3,6,9-trithia-15-azabicyclo[9.3.1]pentadeca-1(15),11,13-triene, **6** (0.017 g, 0.05 mmol) in DCM (4 mL). Slow evaporation of the solution the title compound as a colourless powder. Yield 0.025 g (93%), mp 211-213 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.50 - 2.51 (4H, m), 2.75-2.77 (4H, m), 4.17 (4H, s), 7.74 (2H s). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 29.9, 31.0, 36.3, 126.8, 133.5, 157.5. $\tilde{\nu}_{max}$ (ATR): 3043, 2960, 1560, 1481, 1356, 1319, 1303 cm^{-1}. MS (ES-): m/z $[M+H]^-$ 504.8. Accurate Mass $[C_{11}H_{14}N_2Ag_1S_3BrO_3]^-$ requires 503.8401 found 503.8400. Microanalysis: $C_{11}H_{14}BrAgN_2O_3S_3$ requires: C, 26.0.; H, 2.7; N, 5.5%; found: C, 25.8; H, 2.6; N, 5.6%.

Synthesis of silver(I) complex, 17.

A solution of silver nitrate (0.008 g, 0.05 mmol) in methanol (4 mL) was added slowly, over a period of 20-25 minutes at room temperature to a solution of **(*E*)**-1-(4-((4-methoxyphenyl)diazenyl)phenyl)-3,6,9-trithia-1(2,6)-pyridinacyclodecaphane, **13** (0.023 g, 0.05 mmol) in DCM (4 mL). Slow evaporation of the solution afforded the *title complex* as a red-coloured solid. Yield 0.098 g (90%), mp 260-263 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.50-2.54 (4H, m), 2.74 - 2.83 (4H, m), 3.87 (3H, s), 4.23 (4H, br. s.), 7.16 (2H, d, *J* = 9 Hz), 7.91 (2H, s), 7.94 (2H, d, *J* = 8.8 Hz), 8.01 (2H, d, *J* = 9 Hz), 8.08 (2H, d, *J* = 8.8 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 30.1, 31.2, 37.4, 55.8, 114.8, 121.8, 123.1, 125.0, 128.3, 128.8, 131.5, 132.2, 137.8, 148.1, 156.9. $\tilde{\nu}_{max}$ (ATR): 2974, 2928, 1597, 1549, 1445, 1378, 1308, 1254 cm^{-1}. MS (ES^+): $[M]^+$ 576.5.

Synthesis of Cu(II) complex, 18.

A solution of copper nitrate pentahydrate (0.012 g, 0.05 mmol) in methanol (4 mL) was added slowly, over a period of 20-25 minutes at room temperature, to a solution of 3,6,9-trithia-

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1(2,6)-pyridinacyclodecaphane, **8** (0.013 g, 0.05 mmol) in DCM (4 mL). Slow evaporation of the solution afforded the *title complex*, as a dark green-coloured crystalline solid. Yield 0.021 g (91%), mp 225-226 °C. $\tilde{\nu}_{max}$ (ATR): 3028, 2995, 1434, 1418, 1353, 1262 cm^{-1}. MS (ES^+): $[M]^+$ 443.91. Microanalysis: $C_{11}H_{17}CuN_3O_7S_3$ requires: C, 28.5.; H, 3.7; N, 9.0, S 20.3 %; found: C, 28.7; H, 3.8; N, 9.0, S, 20.1%.

Synthesis of Cu(II) complex, 19.

A solution of copper nitrate pentahydrate (0.012 g, 0.05 mmol) in methanol (4 mL) was added slowly, over a period of 20-25 minutes at room temperature to a solution of 13-Bromo-3,6,9-trithia-15-azabicyclo[9.3.1]pentadeca-1(15),11,13-triene (0.017 g, 0.05 mmol) in DCM (4 mL). Slow evaporation of the solution afforded the *title compound* as a dark-green coloured crystalline solid. Yield 0.025 g (92%), mp 252-254 °C. $\tilde{\nu}_{max}$ (ATR): 2977, 2951, 2932, 2163, 1585, 1286, 1228 cm^{-1}. MS (ES^+): $[M+H]^+$ 522.8. Microanalysis: $C_{11}H_{14}BrCuN_3O_7S_3.2H_2O$ requires: C, 23.6; H, 3.2; Br, 14.3; N, 7.50%; found: C, 23.7; H, 3.4; N, Br 14.1; N, 7.3%.

Synthesis of Cu(II) complex, 20.

A solution of copper pentahydrate (0.012 g, 0.05 mmol) was in methanol (4 mL) was added slowly, over a period of 20-25 minutes at room temperature, to a solution of (*E*)-1-(4-((4-methoxyphenyl)diazenyl)phenyl)-3,6,9-trithia-1(2,6)-pyridinacyclodecaphane, **13** (0.023 g, 0.05 mmol) in DCM (4 mL) and copper nitrate (0.012 g, 0.05 mmol) was dissolved in methanol (4 mL). Slow evaporation of the solvent afforded the *title complex* as red-coloured powder. Yield 0.028 g (96%), mp 284-287 °C. $\tilde{\nu}_{max}$ (ATR): 2960, 2926, 1598, 1583, 1498, 1397, 1280, 1247 cm^{-1}. MS (ES^+): $[M]^+$ 530.1.

Synthesis of Hg(II) complex. 21.[5a,5d] 3,6,9-Trithia-1(2,6)-pyridinacyclodecaphane (0.013 g, 0.05 mmol) was dissolved in DCM (4 mL) and $HgCl_2$ (0.025 g, 0.05 mmol) was dissolved in methanol (4 mL) and this solution was added slowly over a period of 20-25 min at room temperature. Slow evaporation of the solution afforded the *title complex* as a colourless, crystalline solid. Yield 0.038 g (95%), mp 221-223 °C (Lit.[19]: 199-201°C). ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 2.44 - 2.58 (8H, m), 3.85 (4H, s), 7.37 (2H, d, *J* = 7.5 Hz), 7.75 (1H, t, *J* = 7.6 Hz). ^{13}C NMR (125 MHz, CD_2Cl_2) δ ppm 30.5, 31.5, 36.7, 122.7, 139.2, 158.1. $\tilde{\nu}_{max}$ (ATR): 3105, 2989, 1461, 1383, 1371, 1339 cm^{-1}.

Synthesis of Hg(II) complex, 22.

Mercury(II) iodide (0.023 g, 0.05 mmol) was dissolved in methanol (4 mL) and this solution was added slowly, over a period of 20-25 minutes at room temperature, to a solution of 13-bromo-3,6,9-trithia-15-azabicyclo[9.3.1]pentadeca-1(15),11,13-triene, **6** (0.017 g, 0.05 mmol) in DCM (4 mL). Slow evaporation of the solvent afforded the *title compound* as a colourless crystalline solid. Yield 0.058 g (84%), mp 216-218 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 2.54 (8H, br. s), 3.81 (4H, s), 7.54 (2H, s). ^{13}C NMR (125 MHz, CD_2Cl_2) δ ppm 30.5, 31.5, 36.3, 125.9, 135.4, 159.7. $\tilde{\nu}_{max}$ (ATR): 3038, 2887, 1564, 1555, 1394, 1376, 1250 cm^{-1}. MS (ES^+): $[M]^+$ 536.9.

Synthesis of Hg(II) complex, 23.

(*E*)-1-(4-((4-methoxyphenyl)diazenyl)phenyl)-3,6,9-trithia-1(2,6)-pyridinacyclodecaphane (0.023 g, 0.05 mmol) was dissolved in DCM (4 mL) and mercury iodide (0.023 g, 0.05 mmol) was dissolved in methanol (4 mL) and this solution was added slowly over a period of 20-25 min at room temperature. Slow evaporation of the solvent afforded the *title complex* as a yellow-coloured crystalline solid. Yield 0.065 g (95%), mp 226-228 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.61 - 2.68 (8H, m, Ar-$H_{13,14}$) 3.92 (3H, s, OCH_3) 3.97 (4H, s), 7.05 (2H, dd, *J*=8.8, 2.2 Hz), 7.67 (2H, s), 7.98 (2H, dd, *J* = 8.8, 2.5 Hz), 8.01 (2 H, d, *J* = 8.8 Hz), 8.05 (2H, d, *J* = 8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 30.1, 31.1, 36.7, 55.6, 114.3, 120.0, 123.3, 125.0, 127.8, 133.1, 153.1, 162.4. $\tilde{\nu}_{max}$(ATR): 2945, 2914, 1596, 1578, 1481, 1367, 1317, 1248 cm^{-1}. MS (ES^+): $[M]^+$ 669.9.

Blank experiment with TFA (In situ Formation of trifluoroacetate salt, 24. To a solution of **13** (20 mg) in CD_2Cl_2 (1 mL) was added 1 drop of TFA at ambient temperature. ^{1}H NMR (400 MHz, CD_2Cl_2) δ ppm 2.56 - 2.62 (4H, m), 2.72 - 2.78 (4H, m, Ar-H), 3.92 (3H, s), 4.30 (4H, s), 7.08 (2H, dd, *J* = 8.32, 2.0 Hz,), 7.97 - 8.01 (4H, m), 8.10 (2H, dd, *J* = 8.3, 1.7), 8.14 (2H, s). ^{13}C NMR (125 MHz, CD_2Cl_2) δ ppm 31.7, 32.4, 33.1, 56.6, 115.3, 124.1, 124.6, 126.2, 129.8, 135.8, 147.8, 155.0, 155.7, 158.4, 164.0.

Conclusions

In summary, we have synthesised and fully characterised a new azo dye-macrocycle conjugate, **13**, which incorporates an "S_3N" macrocycle as a metal binding site. Complexation of **6**, **8** and **13** to Ag(I), Hg(II) and Cu(II) affords well defined complexes of which have been fully characterised. Complexation of transition metals to ligand **13** results in a small bathochromic shift its UV spectrum, which is most pronounced in the case of Cu(II) ($\Delta\lambda$ = 14 nm): similar bathochromic shifts have been reported upon complexation of quinolone-functionalisized azo dyes.[3i] In contrast, DFT calculations indicate that ligation of metals by the ligand **13** should result in a hypsochromic shift in λ_{max} in the UV-visible spectrum, and that such changes are metal-dependent. Studies are now underway in order to define second generation systems which incorporate other, more responsive, reporter functionality for biomedical studies.[25]

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Notes and references

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