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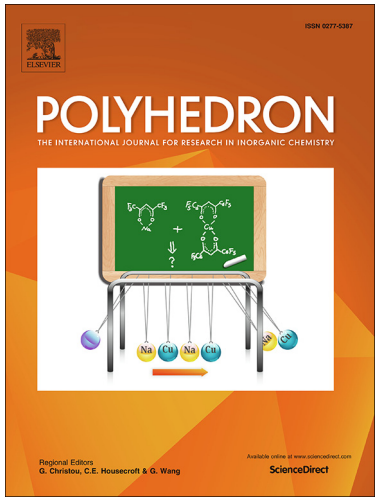

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PII: S0277-5387(19)30528-5
DOI: https://doi.org/10.1016/j.poly.2019.08.003
Reference: POLY 14098

To appear in: *Polyhedron*

Received Date: 1 May 2019
Revised Date: 1 August 2019
Accepted Date: 1 August 2019

Please cite this article as: R.E. Mewis, S.J. Archibald, Side-bridged cyclam transition metal complexes bearing a phenolic ether or a phenolate pendent arm, *Polyhedron* (2019), doi: https://doi.org/10.1016/j.poly.2019.08.003

Side-bridged cyclam transition metal complexes bearing a phenolic ether or a phenolate pendent arm

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1. Abstract

Side-bridged cyclam transition metal complexes (M = Ni(II), Cu(II) and Zn(II)) bearing a phenolic ether or phenolate pendent arm have been synthesised. For $[Ni\mathbf{L^1}]^+$ and $[Cu\mathbf{L^1}]^+$, evidence for a phenoxyl radical was obtained (quasi reversible peak at +0.74 V and +0.48 V respectively), as well as oxidation of OH, due to protonation of the phenolate, at ~+1.24 V. The phenoxyl radical in $[Ni(\mathbf{L^1})]^{2+}$ is harder to oxidise by 0.26 V compared with the corresponding Cu(II) complex. UV-Vis data for $[Ni(\mathbf{L^1})]^{2+}$ suggests that the Ni(II) ion may be 4 or 6 coordinate whereas the Cu(II) ion in $[Cu(\mathbf{L^1})]^{2+}$ is five coordinate. The Ni(II) ion in the crystal structure of $[Ni(\mathbf{L^2})][(ClO_4)_2]$ possesses a distorted square-planar geometry in which the phenolic ether pendent arm is not involved in the coordination sphere. The cyclam ligand in this complex adopts a *trans*-II configuration.

Keywords: macrocyclic ligands / azamacrocycles / cyclam / bioinorganic / coordination chemistry

2. Introduction

Chelators based on tetraazamacrocycles, such as 1,4,8,11-tetraazacyclotetradecane (cyclam), have been utilised in medicine and biology for use as radiopharmaceuticals,[1-4] anti-cancer drugs[5-7], magnetic resonance imaging (MRI) contrast agents,[8,9] combined positron emission tomography (PET)/therapy theranostic compounds,[10-14] and anti-HIV (Human Immunodeficiency Virus) drugs.[15-20]

Cyclam rings bearing pendent arms have been the focus of many research groups.[1,16,21-24] The inclusion of pendent arms in to the ligand framework enables the resulting complex to be specifically engineered towards the desired application.[25,26] The chemical design of the pendent arm can be used to modulate the coordination sphere surrounding the metal to increase stability. Additionally, they can be used to provide attachment points for biomolecules to increase the specificity of the complexes' *in vivo* activity[1] or to act as chromophores[27] to increase quantum yields of luminescence processes/ sensing applications.[28,29] The ability of pendent arms to utilise more than one design feature is exemplified by 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA),[2] an extensively used bifunctional chelator (BFC) for copper radionuclides in clinical imaging and therapy studies involving both antibodies and peptides.

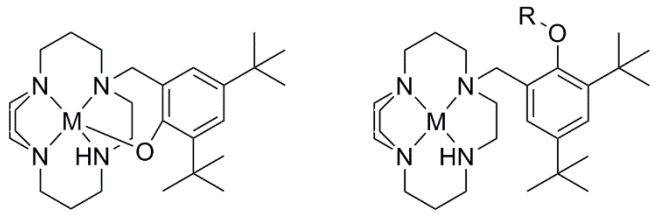
Incorporation of phenolate pendent arms in to cyclam derived chelators is of interest as stabilised phenoxyl radical species can be generated. These radical species are important in a number of copper-containing proteins such as cyctochrome c oxidase, photosystem II and galactose oxidase.[30,31] The complexed metal ion influences the ease of which the phenolate pendent arm can be oxidised and thus, selection of an appropriate metal ion can be used to tune the redox chemistry of the resulting metal complex.[32,33]

Examples of cyclam ligands bearing phenolate pendent arms are known. Nirmala *et al.*[34] have reported on the antimicrobial and electrochemical properties of Cu(II) and Ni(II) dioxocyclam complexes which have phenolate pendent arms. The inclusion of the metal into the macrocyclic cavity elevates antimicrobial and antifungal activity compared with the free ligand. A further example uses 2,4-dimethylphenol as a pendent arm to decorate the periphery of 1,4,7-triazacyclonane to increase the hydrophobicity of the resulting gallium(III) complex in order to study its potential in targeted radiotherapy.[35]

Kimura and co-workers investigated the properties of a phenol containing cyclam ligand synthesised from coumarin.[21,36-40] Several reports on this rigid phenol containing cyclam ligand and its transition metal complexes have been published.[36,39,21] The X-ray structure of the copper(II) complex shows that the phenolic oxygen forms an axial interaction with the copper centre which adopts a five coordinate geometry.[39] An unusually large thermal motion exists between some of the carbon atoms suggesting that the ligand has some flexibility on coordination. The nickel(II) complex shows a significantly lowered redox potential of +0.35 V vs SCE (0.5 M Na_2SO_4, pH 7.5, 25 °C) for $Ni^{III/II}$ with respect to that of nickel(II)-cyclam (+0.50 V vs. SCE), thus highlighting the potential of these complexes to tune metal redox properties.[36] Conversely, the phenol moiety also becomes harder to oxidise upon coordination to nickel(II) (~+0.5 V uncoordinated, ~+0.9 V coordinated).[21]

More recently, Maria *et al.* synthesised rare earth complexes of a dianionic cyclam-based ligand which possessed phenolic pendent arms.[41,42] From X-ray crystallographic studies, the preference for the formation of either distorted octahedral or trigonal prismatic complexes was rationalised by considering the size of the rare earth ion.

Appending pendent arms to the cyclam backbone can be problematic due to the reactivity of the four nitrogen atoms. Consequently routes to circumvent this have been designed,[43-45] such as the inclusion of a bridge by reaction with glyoxal to form the bisaminal.[46-48] The *cis*-configuration of the central two-carbon bridge results in a folded geometry that governs nitrogen reactivity. Two nitrogen atoms have their lone pairs directed towards the convex side of the molecular structure whereas the other two nitrogens have their lone pairs directed towards the concave fold. Mono-alkylation is further favoured as the salt formed after nucleophilic attack precipitates from the reaction mixture. The bisaminal can be reduced in subsequent steps to give the side-bridged cyclam species, which is more rigid than its



ML^1 ML^2 R = Me
ML^3 R = Bn
ML^4 R = *p*-OMeBn

cyclam analogue and, therefore, affords the resulting metal complex increased kinetic stability.[49,50]

Figure 1. Structures of chelators and complexes discussed in this study (M= Ni(II), Cu(II) or Zn(II)).

In this paper we report on the design and synthesis of side-bridged cyclam ligands bearing phenolate (**L^1**) or phenolic ether (**L^2-L^4**) pendent arms and their resulting Ni(II), Cu(II) and Zn(II) complexes, as shown in Figure 1. Through the use of electrochemical and UV-Vis studies, the effect of the chelating ligand on the redox potentials of the Cu(II) and Ni(II) centres are probed and the ease of phenolate moiety oxidation for **L^1** is investigated.

3. Experimental

All chemicals and materials for synthetic procedures were purchased from Sigma Aldrich and used as received. The solvents used were of general purpose or HPLC grade and were purchased from Fisher Scientific. TLC analysis was performed using aluminium-backed silica gel 60 F_{254}, 0.2 (Merck plates) or aluminium-backed aluminium oxide 60 F_{254}, (Merck plates). Silica gel chromatography was performed with silica gel 60 (Davisil). When required diethyl ether, dichloromethane, acetonitrile and acetic acid were dried as follows; diethyl ether was dried over sodium metal and benzophenone followed by distillation; dichloromethane and acetonitrile were dried over calcium hydride for 24 h followed by distillation; acetic acid was dried by adding acetic anhydride (3% w/v) and distilling (b.p. 118°C).

NMR spectra were recorded using a JEOL JNM-LA400 FT NMR spectrometer at a frequency of 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C spectra. Mass spectrometry was performed using a Finnegan MAT 900 XLT system to collect electrospray ionization (ES-MS). Accurate mass spectrometry measurements were obtained using a LTQ Orbitrap XL. UV-Visible spectra were obtained using an Agilent 8453E UV-VIS diode array spectrometer using 1 cm^3 quartz cells.

Single crystal X-ray diffraction data were collected on a Stöe IPDS-II imaging plate diffractometer, using MoKα X-rays of λ=0.71073 Å. Crystals were cooled to 150 K during data collection, with the temperature controlled by an Oxford Systems Cryostream Cooler. Diffraction data were solved using direct methods (SHELXS), and the refinement was by full-matrix least squares against F^2 (SHELXL-97)[51] method. The WinGX program[52] was used for refinement and production of data tables, and the ORTEP-3 program[53] was used for structural visualisation. Hydrogen atoms were fixed in idealised positions and refined using a riding model, with C-H distances of 0.97 Å, N-H distances of 0.91 Å, and U_{iso} 1.5 times U_{eq} of the carrier atom. All ORTEP representations show ellipsoids at the 50% probability level.

Cyclic voltammetry was performed using a standard three-electrode configuration with platinum working (0.2 mm diameter disk) and counter electrodes and a Ag/AgCl reference which gave the $FeCp/ FeCp^+$ couple at 0.55 V using an Autolab II PGSTAT 30 system. All measurements were made in a MeCN argon/nitrogen purged solution containing the metal complex (1 mM) and $[n\text{-}Bu_4N][ClO_4]$ (0.2 M) over the scan rates of 0.01 V s^{-1} to 10 V s^{-1}.

*Synthesis of 3,5-di-tert-butyl-2-methoxybenzaldehyde (**2**)*

K_2CO_3 (1.5 g, 0.011 mol) was suspended in acetone (30 ml) and stirred at RT (room temperature) for 5 min before adding 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.5 g, 0.00214 mol) and MeI (1.3 ml, 0.0214 mol). This yellow mixture was then stirred at RT for 15 hr, by which time the reaction was judged to be complete by TLC (5% ethyl acetate in hexane). The solution was concentrated *in vacuo* and the white solid redissolved in hexane. The potassium carbonate was then removed by filtration and the filtrate concentrated to give **2** as a yellow oil (0.44 g, 83%): R_f = 0.5 (5% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H, CHO), 7.61 (d, 1H, *J*=2.5 Hz, ArH), 7.51 (d, 1H, *J*=2.5 Hz, ArH), 3.82 (s, 3H, OMe), 1.32 (s, 9H, ^{t}Bu), 1.22 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$0 δ 190.7 (CHO), 166.2, 146.2, 142.8, 130.6, 129.0, 124.2 (C_{arom}), 65.9 (OMe), 35.2, 34.6 ($C(^{t}Bu)$), 31.2, 30.8 ($CH_3(^{t}Bu)$); MS (ES-MS): *m/z* 248 (M^+).

*Synthesis of (3,5-di-tert-butyl-2-methoxyphenyl) methanol (**5**)*

2 (0.44 g, 1.77 mmol) was dissolved in ethanol (30 ml) to which was added $NaBH_4$ (0.1 g, 2.63 mmol) portionwise. This yellow solution was then stirred at RT for 2.5 hr before concentrating under reduced pressure prior to partitioning between CH_2Cl_2 (60 ml) and brine (200 ml). The organic layer was collected and dried over $MgSO_4$ before removing the solvent *in vacuo* to give a yellow oil. This was placed in a fridge overnight whereby the oil solidified to give a

white solid (0.44 g, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, 1H, *J*=2.5 Hz, ArH), 7.29 (d, 1H, *J*=2.5 Hz, ArH), 5.26 (s, 1H, OH), 4.74 (s, 2H, CH_2), 3.78 (s, 3H, OMe), 1.40 (s, 9H, ^{t}Bu), 1.31 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 146.0, 141.8, 133.4, 124.4, 123.9 (C_{arom}), 61.9 (OMe), 61.8 (CH_2OH), 35.3, 34.5 (C(^{t}Bu)), 31.5, 31.1 (CH_3(^{t}Bu)); MS (ES-MS): *m/z* 250 (M^+)

*Synthesis of 1-(bromomethyl)-3,5-di-tert-butyl-2-methoxybenzene (**8**)*

5 (0.44 g, 1.41 mmol) was dissolved in $CHCl_3$ (25 ml) at 0°C. PBr_3 (0.38 g, 1.41 mmol) dissolved in $CHCl_3$ (15 ml) was then added dropwise over 30 min under a nitrogen atmosphere. The yellow solution was then stirred at 0°C for a further 1 hr before the organic layer was washed with brine (3 x 200 ml). The organic layer was collected, dried over Na_2SO_4 and concentrated *in vacuo* to give **8** as a yellow oil (0.47, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 1H, *J*=2.5 Hz, ArH), 7.34 (d, 1H, *J*=2.5 Hz, ArH), 4.63 (s, 2H, CH_2), 3.90 (s, 3H, OMe), 1.45 (s, 9H, ^{t}Bu), 1.36 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 146.3, 142.3, 130.7, 127.1, 125.1 (C_{arom}), 62.2 (OMe), 35.4, 34.5 (C(^{t}Bu)), 31.4, 31.1 (CH_3(^{t}Bu)), 23.0 (CH_2Br); MS (ES-MS): *m/z* 312 ($[M-H]^+$), 233 ($[M-Br]^+$).

*Synthesis of 2-(benzyloxy)-3,5-di-tert-butylbenzaldehyde (**3**)*

3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (4.0 g, 0.0171 mol) and potassium carbonate (2.1 g, 0.0171 mol) were dissolved in DMF (25 ml) at 0°C and stirred for 5 min. To the yellow solution was added benzyl bromide (2.89 g, 0.0168 mol) and the resulting mixture was heated to 75°C for 24 hr before cooling and pouring into ice-water (200 ml). The precipitate formed by this process was then collected by filtration and washed with water (2 x 10 ml) to give **3** as fine crystals (5.0 g, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H, CHO), 7.75 (d, 1H, *J*=2.5 Hz, ArH), 7.66 (d, 1H, *J*=2.5 Hz, ArH), 7.51-7.36 (m, 5H, Bn), 5.04 (s, 2H, CH_2), 1.46 (s, 9H, ^{t}Bu), 1.34 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8 (CHO), 159.7, 146.6, 143.1, 136.6, 131.0, 129.3, 128.6, 128.1, 127.0, 124.0 (C_{arom}), 80.4 (CH_2), 35.4, 34.7 (C(^{t}Bu)), 31.3, 30.9 (Me(^{t}Bu)); MS (ES-MS): *m/z* 354 (M^+).

*Synthesis of (2-(benzyloxy)-3,5-di-tert-butylphenyl)methanol (**6**)*

To a solution of **3** (4.50 g, 0.0139 mol) dissolved in methanol (50 ml) was added $NaBH_4$ (1.05 g, 0.0278 mol) portion wise over 5 min. After addition was complete, the yellow solution was stirred at RT for an hour before removing the solvent in vacuo. The white solid formed was then partitioned between $CHCl_3$ (50 ml) and brine (200 ml). The organic layer was collected and further washed with brine (2 x 200 ml). The organic extracts were then combined, dried over $MgSO_4$ and concentrated *in vacuo* to give **6** as a pale yellow oil (4.50 g, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.30 (m, 7H, ArH), 4.97 (s, 2H, CH_2, CH_2Bn), 4.74 (s, 2H, CH_2OH), 1.43 (s, 9H, ^{t}Bu), 1.32 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 146.2, 142.1, 137.6, 133.7, 128.5, 127.6, 126.8, 124.8, 124.1 (C_{arom}), 75.8 (CH_2Bn), 61.5 (CH_2OH), 35.4, 34.5 (C(^{t}Bu)), 31.5, 31.2 (Me(^{t}Bu)); MS (ES-MS): *m/z* 356 (M^+).

*Synthesis of 2-(benzyloxy)-1-(bromomethyl)-3,5-di-tert-butylbenzene (**9**)*

To **6** (2.07 g, 0.00635 mol) in $CHCl_3$ (50 ml) at 0°C under nitrogen was added PBr_3 (1.72 g, 1.5 ml, 0.00635 mol) in $CHCl_3$ (30 ml) over 30 min. The solution was then stirred at 0°C for 1 hr before pouring into brine (200 ml). The organic layer was extracted and then washed further with brine (3 x 200 ml). The organic extracts were combined, dried over Na_2SO_4 and then concentrated *in vacuo* to give **9** as a white solid (2.36 g, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.34 (m, 7H, ArH), 5.12 (s, 2H, CH_2Bn), 4.58 (s, 2H, CH_2Br), 1.43 (s, 9H, ^{t}Bu), 1.32 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 146.5, 142.5, 137.6, 130.9, 128.5, 127.7, 127.3, 126.8, 125.3 (C_{arom}), 75.2 (CH_2Bn), 35.6, 34.5 (C(^{t}Bu)), 31.4, 31.2 (Me(^{t}Bu)), 30.1 (CH_2Br); MS (ES-MS): *m/z* 388 (M^+); Calcd for $C_{14}H_{27}Br_1O_1$: C, 67.90; H, 7.40. Found: C, 68.03; H, 7.63.

*Synthesis of 3,5-di-tert-butyl-2-(4-methoxybenzyloxy)benzaldehyde (**4**)*

3,5-Di-*tert*-butyl-2-hydroxy benzaldehyde (2 g, 0.0085 mol) and K_2CO_3 (1.18 g, 0.0085 mol) in DMF (40 ml) were stirred together for 5 min. 1-(Bromomethyl)-4-methoxybenzene (1.89 g, 0.0094 mol) was then added and the solution heated to 55°C for 24 hr. The reaction mixture was allowed to cool before pouring in to ice-water (60 ml). A precipitate formed which was removed by filtration. The crude solid was then subjected to hot pentane washes (4 x 10 ml). The resulting white solid was then recrystallised from hexane. This gave **4** as colourless crystals (2.11 g, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (CHO), 7.75 (d, 1H, *J*=2.67 Hz, ArH), 7.67 (d, 1H, *J*=2.67 Hz, ArH), 7.43 (d, 2 H, *J*=8.7, ArH), 6.95 (d, 2 H, *J*=8.7, ArH), 4.96 (s, 2H, CH_2Bn), 3.83 (s, 3H, OMe), 1.46 (s, 9H, ^{t}Bu), 1.34 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8 (CHO), 159.7, 159.5, 146.4, 143.0, 130.9, 129.3, 128.7, 128.6, 123.9, 114.0 (C_{arom}), 80.3 (CH_2Bn), 55.2 (OMe), 35.3, 34.7 (C(^{t}Bu)), 31.3, 30.9 (Me(^{t}Bu)); MS (ES-MS): *m/z* 354 (M^+).

*Synthesis of (3,5-di-tert-butyl-2-(4-methoxybenzyloxy)phenyl)methanol (**7**)*

To a solution of **4** (1.5 g, 0.0042 mol) in ethanol (40 ml) was added $NaBH_4$ (0.16 g, 0.0042 mol) portionwise with stirring. The solution was stirred for 3 hours at RT before concentrating the mixture under reduced pressure. The residue was then partitioned between CH_2Cl_2 (100 ml) and water (100 ml). The organic layer was collected, dried over $MgSO_4$ and concentrated under reduced pressure. This gave **7** as a white solid (1.21 g, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H, *J*=8.4 Hz, ArH), 7.37 (d, 1H, *J*=2.5 Hz, ArH), 7.32 (d, 1H, *J*=2.53 Hz, ArH), 6.95 (d, 2H, *J*=8.4 Hz, ArH), 4.91 (s, 2H, CH_2Bn), 4.79 (s, 2H, CH_2OH), 3.82 (s, 3H, OMe), 1.45 (s, 9H, ^{t}Bu), 1.34 (s, 9H, ^{t}Bu); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.2, 153.9, 146.2, 142.1, 133.7, 129.7, 128.6, 124.7, 124.2, 113.9 (C_{arom}), 75.7 (CH_2Bn), 61.8 (CH_2OH), 55.2 (OMe), 35.4, 34.5, (C(^{t}Bu)), 31.5, 31.3, (Me(^{t}Bu)); MS (ES-MS): *m/z* 356 (M^+); Calcd for $C_{23}O_3H_{32}$: C, 77.53; H 8.99. Found C, 77.54; H, 8.73.

*Synthesis of 1-(bromomethyl)-3,5-di-tert-butyl-2-(4-methoxybenzyloxy)benzene (**10**)*

7 (1 g, 0.00281 mol) and CBr_4 (1.4 g, 0.00421 mol) were dissolved in dry CH_2Cl_2 (20 ml) to which was added triphenylphosphine (1.11 g, 0.00421 mol) in dry CH_2Cl_2 (10 ml) over 5 min. A yellow solution formed which was then stirred at RT for 18 hr. Water (150 ml) was then added and the organic layer was extracted. The aqueous layer was further extracted with CH_2Cl_2 (2 x 50 ml). All the organic extracts were combined and dried over $MgSO_4$. The crude product was then purified by silica gel chromatography (1:1 CH_2Cl_2/hexane v/v). The fractions containing the desired compound were then combined and concentrated under reduced pressure to give a light pink solid (0.80 g, 68%); R_f=0.58 (1:1 hexane/ CH_2Cl_2 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, *J*=8.6 Hz, ArH), 7.38 (s, 2H, ArH), 6.89 (d, 2H, *J*=8.6 Hz, ArH), 5.18 (s, 2H, CH_2Bn), 4.63 (s, 2H, CH_2Br), 3.86 (s, 3H, OMe), 1.47 (s, 9H, ^{t}Bu), 1.36 (s, 9H, ^{t}Bu); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.3, 154.2, 146.4, 142.5, 130.9, 129.8, 128.5, 127.3, 126.0, 114.0 (C_{arom}), 75.1 (CH_2Bn), 55.3 (OMe), 35.6, 34.5 (C(^{t}Bu)), 31.6 (CH_2Br), 31.4, 31.3 (Me(^{t}Bu)); MS (ES-MS) m/z 339 ((M-Br)$^+$), 219 ([MH-$C_8H_9O_1Br$]$^+$).

*Synthesis of 2-(bromomethyl)-4,6-di-tert-butylphenyl acetate (**11**)*

To solution of **1** (3.0 g, 0.0100 mol) in acetic anhydride (2.05 g, 0.0201 mol) was added 18 M H_2SO_4 (5 drops). The reaction mixture was stirred for 12 hr at which time the TLC showed complete consumption of the starting material (silica plate using 5% EtOAc in hexane as the eluent). CH_2Cl_2 (50 ml) was then added and the mixture washed with brine (2 x 100 ml). The organic layer was collected and dried over $MgSO_4$ before filtering under reduced pressure. The resulting yellow oil was placed in a freezer whereby a solid formed overnight (3.41 g, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, ArH), 7.32 (s, 1H, ArH), 4.34 (s, 2H, CH_2Br), 2.42 (s, 3H, COMe), 1.37 (s, 9H, ^{t}Bu), 1.33 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (COMe), 148.7, 145.5, 141.4, 130.1, 126.4, 125.6 (C_{arom}), 35.1, 34.8

(C(^{t}Bu)), 31.5, 30.7 (Me(^{t}Bu)), 29.7 (CH_2Br), 21.6 ($COCH_3$); Calcd. for $C_{17}O_2Br_1H_{25}$: C, 59.82; H, 7.33. Found: C, 60.11; H, 7.52; MS (ES-MS): *m/z* 261 ([M-Br]$^+$), 219.2 ([MH-CH_3OBr]$^+$).

*Synthesis of N-3,5-di-tert-butyl-2-methoxy-benzyl-cis-3a,5a,8a,10a-tetraazaperhydropyrene bromide (**14**)*

12 (0.21g, 0.959 mmol) and **8** (0.3g, 0.958 mmol) were dissolved in dry MeCN (20 ml) and stirred at RT for 5 days. The solvent was removed in vacuo and the residue washed with diethyl ether (30 ml). A precipitate formed which was collected by filtration and washed with further ether (3 x 10 ml). This gave the product as a white solid (0.33 g, 64%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, 1H, *J*=2.2 Hz, ArH), 7.33 (d, 1H, *J*=2.2 Hz, ArH), 4.76 (s, 5H, CH_2), 4.21-4.15 (m, 2H, CH_2), 3.72-3.49 (m, 1H, CH_2), 3.40-3.33 (m, 1H, CH_2), 3.21-2.87 (m, 12H, CH_2 and OMe), 2.55-2.15 (m, 6H, CH_2), 1.33 (s, 9H, ^{t}Bu), 1.24 (s, 9H, ^{t}Bu);^{13}C NMR (100 MHz, CD_3OD) δ 155.1, 143.8, 140.6, 126.7, 124.9, 117.1 (C_{arom}), 80.1, 73.1 (N<u>CH</u>N), 67.3 (O<u>Me</u>), 60.0 (N<u>CH_2</u>Ph), 55.9, 55.6, 51.5, 50.9, 49.1, 48.9, 45.9, 39.3 (CH_2), 32.0, 31.0 (C(^{t}Bu)), 27.2, 27.1 (Me(^{t}Bu)), 15.7, 15.6 (NCH_2<u>CH_2</u>CH_2N); MS (ES-MS): *m/z* 455.7 (M$^+$).

*Synthesis of N-3,5-di-tert-butyl-2-benzylether-benzyl-cis 3a,5a,8a,10a-tetraazaperhydropyrene (**15**)*

12 (0.45 g, 0.002 mmol) and **9** (0.78 g, 0.002 mmol) were dissolved in MeCN (30 ml) and stirred at RT for 3 days. The MeCN was then removed in vacuo and the isolated oil was triturated diethyl ether (30 ml) to yield a white solid. This white solid was then filtered off and further washed with ether (2 x 30 ml) to give **38** as a white solid (0.38 g, 66%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.67-7.35 (m, 7H, ArH), 4.13-4.05 (m, 1H, CH_2), 3.59-2.80 (m, 12H, CH_2), 3.04-2.80 (m, 9H, CH_2), 2.52-2.03 (m, 4H, CH_2), 1.34 (s, 9H, ^{t}Bu), 1.26 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, CD_3OD) δ 153.2, 143.9, 140.4, 133.4, 126.9, 125.3, 124.9, 124.8, 123.9, 117.0 (C_{arom}), 80.3, 74.7 (N<u>CH</u>N), 72.9 (OCH_2Ph), 66.9 (NCH_2Ph), 56.1, 55.9, 50.8, 50.7, 49.0, 48.4, 39.0 (CH_2), 32.0, 30.9 (C(^{t}Bu)), 27.3, 27.0 (Me(^{t}Bu)), 15.5, 15.2 (NCH_2<u>CH_2</u>CH_2N); MS (ES-MS): *m/z* 532.4 (M$^+$).

*Synthesis of 3a-3,5-di-tert-butyl-2-(4-methoxy-benzyloxy)-benzyl-decahyro-5a, 8a, 10a-triaaza-3a-azonia-pyrene bromide (**16**)*

12 (0.53 g, 2.4 mmol) and **10** (1 g, 2.4 mmol) were dissolved in dry MeCN (20 ml) and stirred for 4 days at RT. After this time, a precipitate had formed. The reaction mixture was then concentrated under reduced pressure and filtered. The solid was then washed with pentane (3 x 20 ml), and the product was isolated as an orange solid (1.35 g, 88%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, 1H, *J*=2.4 Hz, ArH), 7.42 (d, 2H, *J*=8.6 Hz, ArH), 7.39 (d, 1H, *J*=2.4 Hz, ArH), 6.94 (d, 2H, *J*=8.6 Hz, ArH), 4.78 (s, 2H, N<u>CH_2</u>Phen); 3.73 (s, 3H, OMe), 3.50-3.20 (m, 6H, CH_2), 3.01- 2.66 (m, 12H, CH_2), 2.37-1.94 (m, 6H, CH_2), 1.41 (s, 9H, ^{t}Bu), 1.26 (s, 9H, ^{t}Bu);^{13}C NMR (100 MHz, CD_3OD) δ 161.5, 158.2, 148.5, 131.4, 130.6, 130.2, 129.6, 121.8, 115.5 (C_{arom}), 85.1, 79.5 (N<u>CH</u>N), 77.7 (O<u>CH_2</u>Phen), 71.6 (N<u>CH_2</u>Phen), 60.6, 55.9, 55.4, 53.7, 53.1, 52.8, 44.8, 43.7 (CH_2 and OMe), 36.7, 35.6 (C(^{t}Bu)), 31.9, 31.7 (Me(^{t}Bu)), 20.2, 19.9 (CH_2<u>CH_2</u>CH_2); MS (ES-MS): *m/z* 562.4 (M$^+$), 222 ((macrocycle)$^+$).

*Synthesis of 3a-(2-acetoxy-3,5-di-tert-butyl-benzyl)-decahydro-5a,8a,10a-triaza-3a-azonia-pyrene bromide (**13**)*

12 (1.36 g, 6.13 mmol) and **11** (2.09 g, 6.13 mmol) were dissolved in dry MeCN (15 ml) and stirred at RT for 3 days. After this period, the reaction mixture was concentrated under reduced pressure and the residue taken up in to diethyl ether (40 ml). A white solid formed which was collected by filtration (2.60 g, 75%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (d, 1H, *J*=2.5 Hz, ArH), 7.48 (br s, 1H, ArH), 4.85 (s, 2H, N<u>CH_2</u>Ph), 4.30 (br s, 2H, CH_2), 3.65-3.59 (m, 2H, CH_2), 3.15-2.96 (br m, 8H, CH_2), 2.69-2.47 (m, 6H, CH_2), 2.38-2.25 (m, 4H, CH_2), 2.02 (s, 3H, COMe), 1.23 (s, 9H, ^{t}Bu), 1.22 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, CD_3OD) δ 170.5 (CO), 149.7, 147.9, 143.2, 128.4, 120.9, 117.2 (C_{arom}), 70.8 (N<u>CH</u>N), 59.7 (N<u>CH_2</u>Ph), 54.8, 54.6, 52.7, 52.5, 42.9 (CH_2), 35.3, 34.9 (C(^{t}Bu)), 30.7, 30.2 (Me(^{t}Bu)), 21.4

(COOMe), 19.3, 19.2 ($CH_2\underline{CH_2}CH_2$); MS (ES-MS): *m/z* 483.3 (M^+).

*Synthesis of 5-(3,5-di-tert-butyl-2-methoxybenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane (**L²**)*

14 (250 mg, 0.467 mmol) was dissolved in ethanol (100 ml) to which was added $NaBH_4$ (0.36 g, 9.3 mmol) portionwise. The solution was then stirred for 7 days at RT before removing the solvent *in vacuo*. The white solid formed was partitioned between CH_2Cl_2 (60 ml) and water (pH 14, 200 ml). The organic layer was collected and dried over Na_2SO_4. The solution was then filtered and the filtrate concentrated under reduced pressure to give **L²** as a yellow oil (190 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, 1H, *J*=2.5 Hz, ArH), 7.11 (d, 1H, *J*=2.5 Hz, ArH), 3.65 (s, 3H, OMe), 3.00-2.13 (m, 26H, CH_2), 1.32 (s, 9H, ^{t}Bu), 1.23 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 145.0, 141.8, 126.6, 123.1 (C_{arom}), 62.4 (O<u>Me</u>), 57.1 (N<u>CH_2</u>Ph), 57.0, 54.5, 54.3, 53.7, 53.4, 51.7, 51.1, 49.8, 48.6, 48.1 (CH_2), 35.3, 34.4 (C(^{t}Bu)), 31.6, 31.3 (Me(^{t}Bu)), 24.0, 19.6 ($NCH_2\underline{CH_2}CH_2N$); MS (ES-MS): *m/z* 460.5 (M^+).

*Synthesis of 5-(2-(benzyloxy)-3,5-di-tert-butylbenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane (**L³**)*

15 (1.09 g, 0.00178 mol) was dissolved in methanol (40 ml) to which $NaBH_4$ (1.36 g, 0.03568 mol) was added portionwise over 5 min. The mixture was then stirred at RT for 2 days before heating to reflux for 2 hr. The solvent was removed under reduced pressure and $KOH_{(aq)}$ (pH 14, 200 ml) added. CH_2Cl_2 (100 ml) was used to extract the organic product which was then dried over $MgSO_4$ and evaporated *in vacuo* to afford **L³** as a yellow oil (0.76 g, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.20 (m, 7H, ArH), 5.19 (s, 2H, NCH_2Bn), 4.82 (s, 2H, OCH_2Bn), 3.70-3.68 (m, 2H, CH_2), 3.28-3.24 (m, 7H, CH_2), 3.12-2.84 (m, 5H, CH_2), 2.56-2.39 (m, 11H, CH_2), 1.36 (s, 9H, ^{t}Bu), 1.23 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) 155.0, 145.4, 142.0, 137.9, 129.9, 128.5, 127.6, 126.7, 126.6, 123.3 (C_{arom}), 77.0 (O<u>CH_2</u>Ph), 56.9 (N<u>CH_2</u>Ph), 54.5, 54.0, 53.6, 51.0, 50.7, 49.7, 48.2, 47.8 (CH_2), 35.4, 34.5 (C(^{t}Bu)), 31.6, 31.3 (Me(^{t}Bu)), 25.6, 23.8 ($NCH_2\underline{CH_2}CH_2N$); MS (ES-MS): *m/z* 536.4 (MH^+).

*Synthesis of 5-[3,5-di-tert-butyl-2-(4-methoxy-benzyloxy)-benzyl]-1,5,8,12-tetraaza-bicyclo[10.2.2]hexadecane (**L⁴**)*

To **16** (1 g, 1.56 mmol) dissolved in EtOH (50 ml) was added $NaBH_4$ (1.18 g, 31.20 mmol) portionwise. A colour change from yellow to colourless occurred during this addition. The mixture was then left for 2 weeks stirring at RT, before concentrating under reduced pressure. The residual solid was then partitioned between CH_2Cl_2 (50 ml) and $KOH_{(aq)}$ (pH 14, 200 ml). The organic layer was then collected and dried over $MgSO_4$ before concentrating under reduced pressure. The product was obtained as a yellow oil (0.85 g, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2H, *J*=8.4 Hz, ArH), 7.32 (s, 1H, ArH), 7.23 (s, 1H, ArH), 6.86 (d, 2H, *J*=8.4 Hz, ArH), 4.73 (s, 2H, O<u>CH_2</u>Phen), 3.70 (s, 3H, OMe), 3.65 (s, 2H, N<u>CH_2</u>Phen), 3.05-2.99 (m, 1H, CH_2), 2.78 (br s, 6H, CH_2), 2.56-2.35 (m, 12H, CH_2), 2.21-1.94 (m, 6H, CH_2), 1.37 (s, 9H, ^{t}Bu), 1.29 (s, 9H, ^{t}Bu);^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 159.2, 149.5, 145.9, 135.6, 134.3, 132.8, 130.6, 127.1, 117.8 (C_{arom}), 81.5 (O<u>CH_2</u>Phen), 61.4, 59.4, 58.2, 58.1, 57.8, 57.5, 55.6, 53.6, 52.4, 49.3 (CH_2 and OMe), 39.6, 38.7 (C(^{t}Bu)), 35.8, 35.5 (Me(^{t}Bu)), 24.3, 23.01 ($CH_2\underline{CH_2}CH_2$); MS (ES-MS): *m/z* 566.3 (MH^+).

*Synthesis of acetic acid 2,4-di-tert-butyl-6-(1,5,8,12-tetraaza-bicyclo[10.2.2]hexadec-5-ylmethyl)phenyl ester (**17**)*

13 (2.6 g, 4.62 mmol) was dissolved in ethanol (150 ml) to which was added $NaBH_4$ (3.51 g, 92.4 mmol) portion wise. The reaction mixture was stirred at RT overnight at which time hydrogen evolution had ceased. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between CH_2Cl_2 (100 ml) and $KOH_{(aq)}$ (pH 14, 200 ml). The organic layer was then collected and dried over $MgSO_4$. The filtrate was then concentrated under reduced pressure before dissolving in the minimal amount of acetone (~10 ml) which was triturated with pentane (150 ml) to give a cream solid which was collected by filtration (2.20 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2H, *J*=2.5 Hz, ArH), 7.24 (d, 2H, *J*=2.5 Hz, ArH), 5.23 (s, 2H, CH_2), 3.33-2.37 (m, 28H, CH_2 and NH), 2.25 (s, 3H,

COOMe), 1.27 (s, 9H, ^{t}Bu), 1.25 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (CO), 144.1, 142.3, 136.8, 127.9, 122.0, 119.3 (C_{arom}), 53.8, 53.4, 51.4, 49.9, 48.3, 47.9, 45.0, 46.0, 45.5, 44.8, 43.5 (CH_2), 31.2, 31.1 (C(^{t}Bu)), 27.7, 26.8 (Me(^{t}Bu)), 23.1, 22.8, ($CH_2CH_2CH_2$), 20.8 (COOMe); HRMS (ES-MS) expected for $C_{29}H_{50}N_4O_2H$: 487.4007, found 487.3996.

*Synthesis of 2,4-di-tert-butyl-6-(1,5,8,12-tetraaza-bicyclo[10.2.2]hexadec-5-ylmethyl)-phenol hydrochloride salt (**L¹**)*

To **17** (1.5 g, 3.09 mmol) dissolved in MeOH (10 ml) was added 6M $HCl_{(aq)}$ (10 ml). This induced a colour change from yellow to colourless. The solution was then heated to reflux for 24 hr before cooling to room temperature. The solution was concentrated under reduced pressure, and the addition of acetone (30 ml) caused a yellow precipitate to form. This was collected by filtration and dried *in vacuo* (1.44 g, 79%); ^{1}H NMR (400 MHz, D_2O) δ 7.24 (s, 1H, ArH), 7.16 (s, 1H, ArH), 3.40-3.14 (m, 15H, CH_2 and NH), 2.02-1.80 (m, 10H, CH_2), 1.11 (s, 9H, ^{t}Bu), 1.01 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, D_2O) δ 151.7, 144.4, 140.1, 127.7, 125.6, 120.5 (C_{arom}), 74.3 (NCH_2Phen), 49.2, 48.8, 48.2, 48.0, 47.8, 46.8, 46.0 (CH_2), 34.6, 33.9 (C(^{t}Bu)), 30.7, 29.5 (Me(^{t}Bu)), 21.5, 20.7 ($CH_2CH_2CH_2$); HRMS (ES-MS) expected for $C_{27}H_{48}N_4OH$: 445.3901, found 445.3891.

*Synthesis of copper(II) 5-(3,5-di-tert-butyl-2-methoxybenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane perchlorate ([Cu**L²**](ClO₄)₂)*

To a solution of **L²** (100 mg, 0.218 mmol) in MeOH (10 ml) was added copper(II) perchlorate hexahydrate (0.08 g, 0.218 mmol) in MeOH (3 ml). The blue solution was then heated to reflux for 2 hr. After this time the solution was allowed to cool, filtered and concentrated under reduced pressure to give a blue-purple crystalline solid (154 mg, 98%); HRMS (ES-MS) expected for $C_{28}N_4H_{50}O_5Cl_1Cu_1$: 620.2760, found 620.2767; ε (MeOH): 547 nm (331 $mol^{-1}dm^3$ cm^{-1}).

*Synthesis of zinc(II) 5-(3,5-di-tert-butyl-2-methoxybenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane perchlorate ([Zn**L²**](ClO₄)₂)*

To a solution of **L²** (100 mg, 0.218 mmol) in MeOH (10 ml) was added zinc(II) perchlorate hexahydrate (0.08 g, 0.218 mmol) in MeOH (3 ml). The yellow solution was then heated to reflux for 2 hr. After this time the solution was allowed to cool, filtered and concentrated under reduced pressure to give a white crystalline solid (150 mg, 95%); ^{1}H NMR (400 MHz, CD_3CN) δ 7.14 (d, 1H, *J*=2.5 Hz, ArH), 7.10 (d, 1H, *J*=2.5 Hz, ArH), 3.64 (s, 3H, OMe), 2.99-2.11 (m, 26H, CH_2), 1.33 (s, 9H, ^{t}Bu), 1.25 (s, 9H, ^{t}Bu); ^{13}C NMR (400 MHz, CD_3CN) δ 157.5, 145.1, 141.5, 125.7, 124.3 (C_{arom}), 62.9 (OMe), 57.8 (NCH_2Ph), 56.5, 54.4, 54.3, 53.7, 53.3, 51.6, 51.2, 49.8, 48.7, 48.1 (CH_2), 35.5, 34.7 (C(^{t}Bu)), 31.6, 31.6 (Me(^{t}Bu)), 24.1, 19.6 ($NCH_2CH_2CH_2N$); HRMS (ES-MS) expected for $C_{28}H_{50}O_5N_4Cl_1Zn_1$: 621.2756, found 621.2763.

*Synthesis of nickel(II) 5-(3,5-di-tert-butyl-2-methoxybenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane perchlorate ([Ni**L²**](ClO₄)₂)*

To a solution of **L²** (100 mg, 0.218 mmol) in MeOH (10 ml) was added nickel(II) perchlorate hexahydrate (0.08 g, 0.218 mmol) in MeOH (3 ml). The orange solution was then heated to reflux for 2 hr. After this time the solution was allowed to cool, filtered and concentrated under reduced pressure to give a orange crystalline solid (152 mg, 98%); HRMS (ES-MS) expected for $C_{28}H_{50}N_4ONi$: 258.1664 (M^{2+}) found 258.1665; HRMS (ES-MS) expected for $C_{28}H_{50}N_4ONi$: 615.2818 (M^{+}) found 615.2808; ε (MeOH): 477 nm (197 $mol^{-1}dm^3$ cm^{-1}).

*Synthesis of copper(II) 5-(2-(benzyloxy)-3,5-di-tert-butylbenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane perchlorate ([Cu**L³**](ClO₄)₂)*

To **L³** (100 mg, 0.187 mmol) dissolved in MeOH (10 ml) was added copper(II) perchlorate hexahydrate (0.07 g, 0.187 mmol) in MeOH (3 ml). The blue solution was then heated to reflux for 2 hr. After this time the solution was allowed to cool, filtered and concentrated under reduced pressure to give a purple crystalline solid (130 mg, 87%); HRMS (ES-MS) expected for $C_{34}H_{54}O_5N_4Cl_1Cu_1$: 696.3073, found 696.3075; ε (MeOH): 550 nm (286 mol^{-1} dm^3 cm^{-1}).

*Synthesis of zinc(II) 5-(2-(benzyloxy)-3,5-di-tert-butylbenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane perchlorate ([Zn**L³**](ClO₄)₂)*

To **L³** (100 mg, 0.187 mmol) dissolved in MeOH (10 ml) was added zinc(II) perchlorate hexahydrate (0.0822 g, 0.187 mmol) in MeOH (3 ml). The yellow solution was then heated to reflux for 2 hr. After this time the solution was allowed to cool, filtered and concentrated under reduced pressure to give a white crystalline solid (0.0702 mg, 47%); ^{1}H NMR (400 MHz, CD_3CN) δ 7.46-7.22 (m, 7H, ArH), 5.21 (s, 2H, NCH_2Bn), 4.79 (s, 2H, OCH_2Bn), 3.72-3.66 (m, 2H, CH_2), 3.29-3.22 (m, 7H, CH_2), 3.13-2.82 (m, 5H, CH_2), 2.57-2.33 (m, 11H, CH_2), 1.34 (s, 9H, ^{t}Bu), 1.26 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, CD_3CN) 156.1, 144.4, 142.0, 137.6, 129.6, 128.8, 127.5, 126.6, 126.4, 123.3 (C_{arom}), 77.1 ($O\underline{CH_2}Ph$), 56.4 ($N\underline{CH_2}Ph$), 54.5, 53.8, 53.6, 51.1, 50.7, 49.6, 48.2, 47.9 (CH_2), 35.3, 34.7 (C(^{t}Bu)), 31.6, 31.3 (Me(^{t}Bu)), 25.6, 23.8 ($NCH_2\underline{CH_2}CH_2N$); HRMS (ES-MS) expected for $C_{34}H_{54}N_4O_5ZnCl$: 697.3069, found 697.3060.

*Synthesis of nickel(II) 5-(2-(benzyloxy)-3,5-di-tert-butylbenzyl)-1,5,8,12-tetraazabicyclo[10.2.2]hexadecane perchlorate ([Ni**L³**](ClO₄)₂)*

To **L³** (150 mg, 0.281 mmol) dissolved in MeOH (10 ml) was added nickel(II) perchlorate hexahydrate (102 mg, 0.281 mmol) in MeOH (3 ml). The yellow/brown solution was then heated to reflux for 2 hr. After this time the solution was allowed to cool, filtered and concentrated under reduced pressure to give an orange crystalline solid (0.0925 g, 42%); HRMS (ES-MS) expected for $C_{34}H_{54}N_4O_5NiCl$: 691.3131 (M^+), found 691.3122; ε (MeOH): 481 nm (100 mol^{-1} dm^3 cm^{-1}).

*Synthesis of copper(II) 5-[3,5-di-tert-butyl-2-(4-methoxy-benzyloxy)-benzyl]-1,5,8,12-tetraaza-bicyclo[10.2.2]hexadecane perchlorate ([Cu**L⁴**](ClO₄)₂*

To **L⁴** (0.1 g, 0.1773 mmol) dissolved in MeOH (8 ml) was added copper(II) perchlorate hexahydrate (0.657g, 0.1773 mmol) in MeOH (2 ml). The blue solution was heated to reflux for 2 hr before it was allowed to cool to RT. The solution was then concentrated under reduced pressure before redissolving in the minimal amount of MeOH. This solution was then eluted down a Sephadex LH-20 column with MeOH. The blue fraction was isolated and concentrated under reduced pressure. The oily residue was triturated with ether (3 x 5 ml) to afford the title compound as a blue solid (0.0430 g, 29%); HRMS (ES-MS) expected for $C_{35}H_{56}O_2N_4CuClO_4$: 726.3179, found 726.3183; ε (MeOH): 529 nm (154 mol^{-1} dm^3 cm^{-1}).

*Synthesis of nickel(II) 5-[3,5-di-tert-butyl-2-(4-methoxy-benzyloxy)-benzyl]-1,5,8,12-tetraaza-bicyclo[10.2.2]hexadecane perchlorate ([Ni**L⁴**](ClO₄)₂)*

To **L⁴** (0.1 g, 0.1773 mmol) dissolved in MeOH (8 ml) was added nickel(II) hexahydrate (0.0648 g, 0.1773 mmol) in MeOH (2 ml). The orange solution was heated to reflux for 2 hr before it was allowed to cool to RT. The solution was then concentrated under reduced pressure before redissolving in the minimal amount of MeOH. This solution was then eluted on a Sephadex LH-20 column with MeOH. The orange fraction was isolated and concentrated under reduced pressure. The oily residue was triturated with ether (3 x 5 ml) to afford the title compound as an orange solid (0.0640 g, 44%); HRMS (ES-MS) expected for $C_{35}H_{56}O_2N_4NiClO_4$: 721.3236, found 721.3237; ε (MeOH): 478 nm (96 mol^{-1} dm^3 cm^{-1}).

*Synthesis of zinc(II) 5-[3,5-di-tert-butyl-2-(4-methoxy-benzyloxy)-benzyl]-1,5,8,12-tetraaza-bicyclo[10.2.2]hexadecane perchlorate ([Zn**L**^{4}](ClO$_4$)$_2$)*

To **L**^{4} (0.1 g, 0.1773 mmol) dissolved in MeOH (8 ml) was added zinc(II) hexahydrate (0.066 g, 0.1773 mmol) in MeOH (2 ml). The yellow solution was heated to reflux for 2 hr before it was allowed to cool to RT. The solution was then concentrated under reduced pressure before redissolving in the minimal amount of MeOH. This solution was then eluted on a Sephadex LH-20 column with MeOH. The light yellow fraction was isolated and concentrated under reduced pressure. The oily residue was triturated with ether (3 x 5 ml) to afford the title compound as a white solid (0.0720g, 49%); ^{1}H NMR (400 MHz, CD_3CN) δ 7.35 (d, 2H, *J*=8.7 Hz, ArH), 7.29 (s, 1H, ArH), 7.21 (br s, 1H, ArH), 6.86 (d, 2H, *J*=8.7 Hz, ArH), 4.77 (s, 2H, O$\underline{CH_2}$Phen), 3.69 (s, 3H, OMe), 3.63 (s, 2H, N$\underline{CH_2}$Phen), 3.11-3.01 (m, 1H, CH_2), 2.78 (br s, 6H, CH_2), 2.56-1.92 (m, 18H, CH_2), 1.34 (s, 9H, ^{t}Bu), 1.26 (s, 9H, ^{t}Bu);^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 158.9, 149.2, 146.1, 135.8, 134.3, 132.7, 130.2, 127.4, 117.6 (C_{arom}), 81.5 (O$\underline{CH_2}$Phen), 60.5, 59.3, 58.2, 58.0, 57.8, 56.3, 55.8, 54.6, 52.8, 49.4 (CH_2 and OMe), 39.5, 38.6 (C(^{t}Bu)), 35.7, 35.5 (Me(^{t}Bu)), 24.7, 23.2 ($CH_2\underline{CH_2}CH_2$); HRMS (ES) expected for $C_{34}H_{54}O_2N_4ZnO_4Cl$: 713.3804, found 713.3807.

*Synthesis of copper(II) 2,4-di-tert-butyl-6-(1,5,8,12-tetraaza-bicyclo[10.2.2]hexadec-5-ylmethyl)-phenolate perchlorate ([Cu**L**^{1}]ClO$_4$)*

To **L**^{1} (180 mg, 0.305 mmol) in MeOH (8 ml) was added NEt_3 (150 mg, 1.5 mmol). The reaction mixture was stirred for 5 min, by which time the colour of the solution had changed from yellow to straw colour. To this solution was then added copper(II) perchlorate hexahydrate (113 mg, 0.305 mmol) in MeOH (3 ml). The royal blue solution was then heated to reflux for 2 hr before it was allowed to cool. The reaction mixture was concentrated under reduced pressure to a minimal volume before eluting down a Sephadex LH-20 column using MeOH. The blue fraction was collected and concentrated under reduced pressure. The oil obtained was triturated with ether (3 x 5 ml) to give a hygroscopic blue solid (0.0737 g, 40%); HRMS (ES-MS) expected for (cation-2H)$^{+}$ $C_{27}H_{45}N_4O_1Cu_1$: 504.2884 found 504.2875; ε (MeOH): 641 nm (27 mol^{-1} dm^3 cm^{-1}).

*Synthesis of nickel(II) 2,4-di-tert-butyl-6-(1,5,8,12-tetraaza-bicyclo[10.2.2]hexadec-5-ylmethyl)-phenolate perchlorate ([Ni**L**^{1}]ClO$_4$)*

To **L**^{1} (180 mg, 0.305 mmol) in MeOH (8 ml) was added NEt_3 (150 mg, 1.5 mmol). The reaction mixture was stirred for 5 min, by which time the colour of the solution had changed from yellow to straw colour. To this solution was then added nickel(II) perchlorate hexahydrate (112 mg, 0.305 mmol) in MeOH (3 ml). The orange solution was then heated to reflux for 2 hr before it was allowed to cool. The reaction mixture was concentrated under reduced pressure to a minimal volume before eluting down a Sephadex LH-20 column using MeOH. The orange fraction was collected and concentrated under reduced pressure. The oil obtained was triturated with ether (3 x 5 ml) to give a hygroscopic orange solid (0.0541 g, 30%); HRMS (ES) expected for $C_{27}H_{47}N_4ONi$: 501.3098, found 501.3093; ε (MeOH): 441 nm (12 mol^{-1} dm^3 cm^{-1}).

*Synthesis of zinc(II) 2,4-di-tert-butyl-6-(1,5,8,12-tetraaza-bicyclo[10.2.2]hexadec-5-ylmethyl)-phenolate perchlorate ([Zn**L**^{1}]ClO$_4$)*

To **L**^{1} (180 mg, 0.305 mmol) in MeOH (8 ml) was added NEt_3 (150 mg, 1.5 mmol). The reaction mixture was stirred for 5 min, by which time the colour of the solution had changed from yellow to straw colour. To this solution was then added zinc(II) perchlorate hexahydrate (113 mg, 0.305 mmol) in MeOH (3 ml). The straw coloured solution was then heated to reflux for 2 hr before it was allowed to cool. The reaction mixture was concentrated under reduced pressure to a minimal volume before eluting down a Sephadex LH-20 column using MeOH as the eluent. The yellow fraction

was collected and concentrated under reduced pressure. The oil obtained was triturated with ether (3 x 5 ml) to give a hygroscopic white solid (0.0530 g, 29%); ^{1}H NMR (400 MHz, CD_3CN) δ 7.63 (s, 1H, ArH), 7.53 (s, 1H, ArH), 4.10-4.09 (m, 2H, $\underline{CH_2}Ph$), 3.26-2.09 (m, 25H, NH and CH_2), 1.31 (s, 9H, ^{t}Bu), 1.22 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, CD_3CN) δ 152.4, 138.6, 138.0, 136.4, 132.6, 129.7 (C_{arom}), 68.8 (CH_2Ph), 51.2, 50.4, 48.3, 48.2, 48.2, 48.1, 47.9 (CH_2), 31.6, 31.0 (C(^{t}Bu)), 30.3, 29.9 (Me(^{t}Bu)); HRMS (ES) expected for $C_{27}H_{47}N_4OZn$: 507.3036, found 507.3036.

4. Results and Discussion

Pendent arm synthesis

Pendent arms incorporating a protected phenol and an alkyl bromide were required to form the desired ligand complexes as outlined in Figure 1. Bromomethyl phenol derivatives were targeted for subsequent tethering to glyoxal bridged cyclam (bisaminal). 2-(Bromomethyl)-4,6-di-*tert*-butylphenol, **1**, was synthesised using a modified literature method reported by Wieghardt and co-workers.[54] Methyl-protected di-*tert*-butyl benzyl bromide (**8**) was synthesised in three steps. The methyl protecting group was introduced using basic media in conjunction with methyl iodide. The aldehyde was then reduced using $NaBH_4$ to form the alcohol (**5**), which was then brominated using PBr_3 in $CHCl_3$ to give **8**. There are limited procedures available for cleaving methyl ethers,[55] and as a result benzyl ethers, which are easier to cleave, were also synthesised.

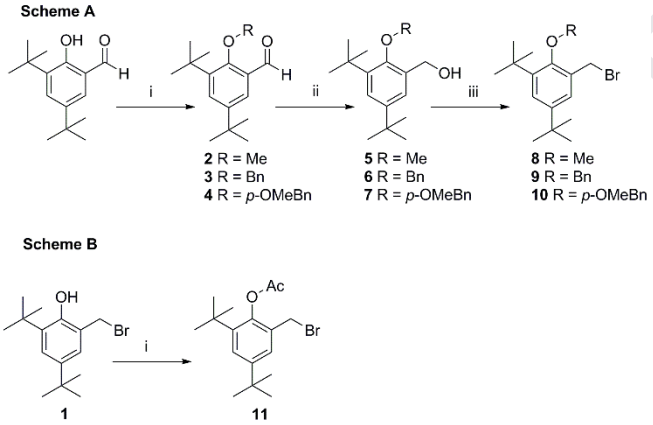


Figure 2. Synthesis of pendent arms; Scheme A : i) acetic anhydride, cat. H_2SO_4, RT 12 hr; ii) K_2CO_3, RX (X = I or Br), RT to 75°C, 15 – 24 hr; iii) $NaBH_4$, RT, 1 – 3 hr; Scheme B : i) PBr_3, $CHCl_3$ (R = Me or Bn), 0°C 1 – 2.5 hr or CH_2Cl_2, PPh_3, CBr_4 (R = *p*-OMeBn), RT, 18 hr.

The benzyl group was introduced by reaction with 2,4-di-*tert*-butyl-2-hydroxy benzaldehyde in the presence of potassium carbonate using DMF to give **3** as the product. A similar type of reaction has been reported by Counsell and co-workers in the synthesis of di-substituted 1-phenol-2-propanones,[56] and by Belmar and Jiménez for preparing hindered polyanionic chelating ligands.[57] Crystals of **3** were grown from hexane by evaporation; the structure elucidated is shown in Figure 3. The benzene rings in each molecule are rotated perpendicular to one another. This is extended to the asymmetric unit where benzene rings opposite each other are again found to be in a perpendicular arrangement. A similar procedure to the formation of **8** was then used to reduce the aldehyde to form the alcohol which was again brominated using PBr_3 to give **9**.

Synthesis of **10** was carried out in an analogous manner to the synthesis of **9** apart from the bromination step. *p*-Methoxybenzyl cleavage can occur under acidic conditions and so carbon tetrabromide/ PPh_3 were used to produce **13**

in 68% yield after column chromatography.

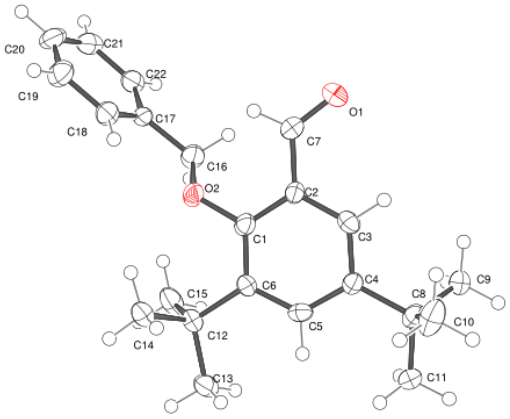
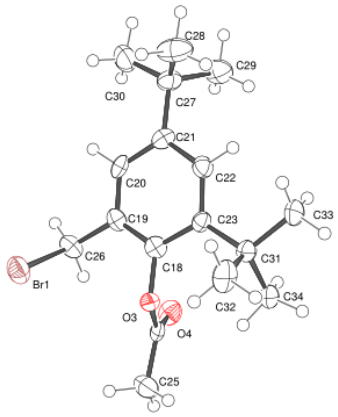


Figure 3. ORTEP representation (50% thermal ellipsoids) of the X-ray crystal structure of **3** with all non-H atoms labelled

The synthesis of **11** was initially attempted using a dimethylaminopyridine (DMAP) coupling between 2,4,-di-*tert*-butyl-2-hydroxy benzaldehyde and Boc_2O.[58] The reaction was judged complete after 3 hr by TLC (R_f = 0.32 in 5% EtOAc/hexane compared with 0.59 for the starting material). However, reduction of the aldehyde using $NaBH_4$ also reduced the ester, reforming the phenol. The acetyl protected phenol compound was instead synthesised from **1**. Wieghardt and co-workers have protected 6-*tert*-butyl-*o*-cresol as the acetyl ester using acetic anhydride at RT with H_2SO_4 as a catalyst.[59] Using the same conditions, **1** was efficiently protected using these conditions and, after an aqueous work-up, **11** was obtained in >95% yield. Crystals of **11** suitable for X-ray crystallography were grown by



evaporation of a toluene solution; the structure is shown in Figure 4.

Figure 4. ORTEP representation (50% thermal ellipsoids) of the X-ray crystal structure of **11** with all non-H atoms labelled.

Functionalised azamacrocycle synthesis

An initial attempt was made to attach **1**, to the bis-aminal cyclam bridged with glyoxal (**12**).[60] Upon the addition of dry

MeCN to a mixture of **1** and **12**, an immediate precipitate formed which was analysed by NMR and mass spectrometry. Analyses provided evidence for **12** acting as a non-nucleophilic base; the precipitate was the hydrobromide salt of cyclam. Focus was, therefore, diverted to the use of the protected phenolate pendent arms.

Reaction of the methyl ether derivative, **8**, with **12** gave the desired mono-alkylated product. This bis-aminal species was then reduced using $NaBH_4$ in ethanol to form the piperazine ring, giving the side-bridged cyclam component, $\mathbf{L^2}$. $\mathbf{L^3}$, $\mathbf{L^4}$ and **17** were synthesised in an analogous way.

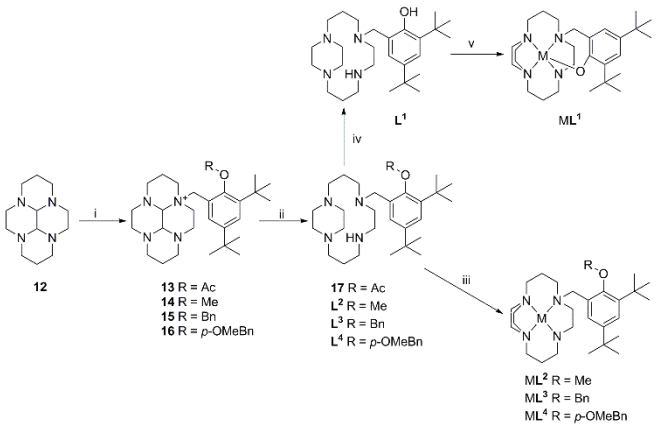


Figure 5. Synthesis of the macrocyclic ligands and their resulting metal complexes (M = Ni, Cu or Zn); i) **8**, **9**, **10** or **11**, MeCN, RT, 3 days; ii) $NaBH_4$, ethanol or methanol, 2 – 7 days, RT; iii) $[M(ClO_4)_2]$, MeOH, 2 hr, reflux; iv) 6 M HCl, 24 hr, reflux; v) NEt_3, $[M(ClO_4)_2]$, MeOH, 2 hr, reflux.

BBr_3 was used in an attempt to unmask the phenol[61] of $\mathbf{L^2}$, under a series of conditions. The temperature was varied between −80°C and RT, and the reaction time was varied, between 2, 4 and 12 hr. A subsequent reaction using the boron-trifluoride ethyl etherate and sodium iodide reagent system[62] was also attempted. Neither route was successful, and this was attibuted to the steric hindrance around the ether group in $\mathbf{L^2}$.

The deprotection of $\mathbf{L^3}$ proved similarly challenging, even though there are a number of methologies for the removal of benzyl protecting groups.[55] Catalytic hydrogenolysis could not be successfully employed as both *N*-benzylic and *O*-benzylic moieties are present, even though conditions similar to those reported for cleaving a benzyl group used to protect 2,4-di-*tert*-butyl phenol linked to an aromatic amine by an amide bond were employed.[57]

A light-initiated process was also attempted. The rapid debenzylation of sterically hindered benzyl ethers is reported by Binkley and Hehemann,[63] which has been further developed by Riley and Grindley.[64] However, the conditions described did not result in the desired product being isolated. A series of other strategies were also attempted. Boron trifluoride ethyl etherate in conjunction with NaI,[62] Amberlyst-15,[65] ferric chloride,[66,67] and acetyl bromide[68] in alcoholic media were all utilised but none of these routes afforded the desired ligand, $\mathbf{L^1}$.

The *p*-methoxybenzyl derivatives offered alternative reactions for the deprotection step. The synthesis of the protected species was again via the bis-aminal intermediate. A variety of methods were attempted including acetic acid at a range of temperatures[69] and cerium chloride hydrate/ sodium iodide.[70] However, $\mathbf{L^1}$ was again not obtained using these deprotection strategies. Hampton and Harmata report that they too were unable to unmask a 2,4-di-tert-butyl moiety in their PHZ (5,6,11,12-tetrahydro-2,8-dimethylphenhomazine) based ligands, so the results reported here for $\mathbf{L^3}$ and $\mathbf{L^4}$ are consistent in this regard.[71]

17 was synthesised *via* our established route and in contrast to the previously synthesised derivatives, the acetyl group could be successfully removed to unmask the phenol. 6 M HCl at reflux was found to be sufficient to cleave the acetyl

protecting group to afford **L¹**.

Complex formation

The Zn(II), Cu(II) and Ni(II) complexes of the phenolic ethers, **L²**, **L³** and **L⁴**, were synthesised and purified by size exclusion chromatography on a Sephadex LH-20 column. Yields for the transition metal complexes of **L²**, **L³** and **L⁴** were in the range of 95-98%, 42-87% and 29-49% respectively.

Orange crystals of the nickel(II) complex of **L²** suitable for X-ray diffraction were grown by evaporating an acetone-ether solution at RT. The oxygen atom from the methoxy group of the pendent arm is not utilised in the coordination to the nickel(II) centre, which adopts a distorted square planar geometry with the four nitrogen atoms of the macrocyclic ring (bond lengths for the nickel(II) ion are given in Table 1). There is disorder in the *tert*-butyl group *para* to the methoxy group, with each atom occupying two sites ~50% of the time (only one site shown in Figure 6). This structure contrasts with the Ni(II) cyclam complex bearing a pendent phenolate arm reported by Iitaka *et al*[21], in which the Ni(II) centre is octahedral. The oxygen of the phenolate fills one apical site with a Ni-O bond length of 2.015 Å. This distance is shorter than the four Ni-N bond lengths (2.072, 2.051, 2.085 and 2.078 Å) and far shorter than apical bond lengths in octahedral nickel(II)-cyclam complexes[72,73] (2.492 Å for X = Cl, 2.169 Å for X = NO_3). The other apical site is filled by an oxygen of a perchlorate anion, which has a bond length of 2.402 Å. The rigidity of the side-bridged cyclam in [Ni**L²**]²⁺ results in a contraction of the Ni-N bond length by ~0.1 Å. The cyclam ligand adopts a *trans*-II configuration which is conistent with all other piperazino methyl cyclam-based chelators.[50] To our knowledge, [Ni**L²**]²⁺, is the first reported side-bridged cyclam based species with a central Ni(II) ion.

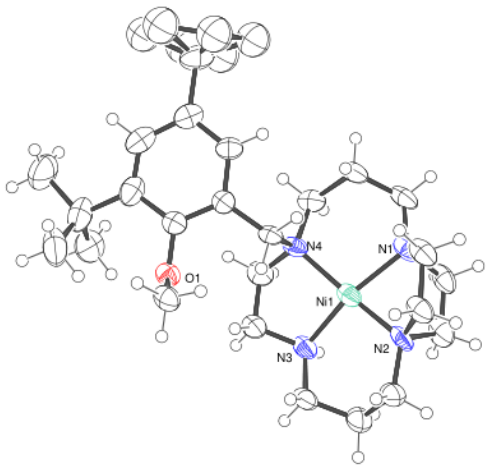


Figure 6. ORTEP representation (50% thermal ellipsoids) of the X-ray crystal structure of [Ni**L²**]²⁺ with all non-H atoms labelled. Water molecules and perchlorate anions have been removed for clarity

Table 1. Selected bond lengths from the X-ray crystal structure of [Ni**L²**]$(ClO_4)_2$.

	Bond length (Å)
Ni(1)-N(1)	1.941(5)
Ni(1)-N(2)	1.922(6)
Ni(1)-N(3)	1.921(5)

Ni(1)-N(4)	1.953(5)

Complexation reactions of **L¹** to Cu(II), Ni(II) and Zn(II) were performed in basic media to ensure deprotonation of the phenol. These complexes are very hygroscopic, and were isolated as oils in yields ranging between 29 – 40%. The ^{1}H NMR spectrum of $[Zn\mathbf{L^1}]^{+}$ possessed the furthest downfield chemical shifts for the two aromatic protons in the phenol ring compared to the analogous complexes **L²-L⁴**.

UV-Vis spectroscopy

UV-Vis data for the Cu(II) and Ni(II) complexes of **L¹-L⁴** are presented in table 2. The electronic spectrum of $[Ni\mathbf{L^2}]^{2+}$ would suggest that the ion is square planar as a single *d-d* transition was observed at 477 nm. Lindoy and co-workers[74] observed only one band for their *N*-benzylated cyclam complexes in the region of 474-488 nm, all of which were square planar. $[Cu\mathbf{L^2}]^{2+}$ also possesses one *d-d* band at 547 nm in the UV, which is diagnostic of a copper(II)-N_4 chromophore, in which solvent or anion may occupy axial positions.[75] However, the featureless nature of the spectrum results in it being of little use for the assignment of a detailed coordination geometry around the copper(II) ion.

Table 2. Tabulated UV-Vis data for the Cu(II) and Ni(II) complexes of **L¹-L⁴**

Complex	λ_{max} / nm	ε / mol^{-1} dm^3 cm^{-1}
$[Cu\mathbf{L^1}](ClO_4)$	641	27
$[Cu\mathbf{L^2}](ClO_4)_2$	547	331
$[Cu\mathbf{L^3}](ClO_4)_2$	550	286
$[Cu\mathbf{L^4}](ClO_4)_2$	529	154
$[Ni\mathbf{L^1}](ClO_4)$	441	12
$[Ni\mathbf{L^2}](ClO_4)_2$	477	197
$[Ni\mathbf{L^3}](ClO_4)_2$	481	100
$[Ni\mathbf{L^4}](ClO_4)_2$	478	96

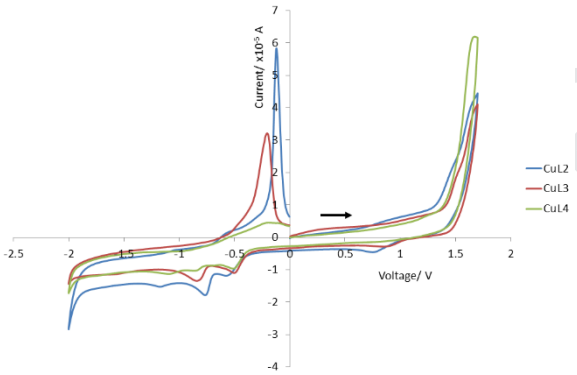
Electronic spectra of $[Cu\mathbf{L^3}]^{2+}$ and $[Ni\mathbf{L^3}]^{2+}$ were similar to the analogous complexes formed with **L²**. Two single *d-d* bands were observed at 550 and 481 nm for the copper(II) and nickel(II) complexes respectively. $[Ni\mathbf{L^3}]^{2+}$ is, therefore, square planar whereas it is again difficult to ambiguously assign the coordination around the copper(II) ion in $[Cu\mathbf{L^3}]^{2+}$. Similar electronic spectra were observed for the copper(II) and nickel(II) complexes of **L⁴**; two single *d-d* bands were again observed at 529 and 478 nm for the copper(II) and nickel(II) complexes respectively. The presence of the different phenolic ethers produced would, therefore, appear to have little effect on the coordination sphere around the metal centre.

However, the electronic spectrum of $[Cu\mathbf{L^1}]^{+}$ displayed a single *d-d* transition at 641 nm. The shift observed is indicative of a five-coordinate geometry (either distorted square based pyramidal or trigonal bipyramidal) being formed around the metal ion.[76] This would imply that the phenolate ligand occupies the apical site in solution. The electronic spectrum of $[Ni\mathbf{L_1}]^{+}$ possesses one strong *d-d* transition at 441 nm and a weaker one at 581 nm. In the nickel(II) complex of a phenolate cyclam ligand produced by Kimura and co-workers,[40] different absorptions are

observed dependent on pH. At acidic and basic pH, absorptions at 424 and 559 nm were observed respectively, corresponding to a transition from low spin to high spin.[77] This data suggests that in the nickel(II) complex of **L**^{1}, the nickel(II) ion adopts either a square planar geometry with the phenol not bound to the metal centre, or an octahedral geometry in which the phenol is bound to the metal in the axial site and a solvent molecule occupies the remaining site.

Cyclic voltammetry

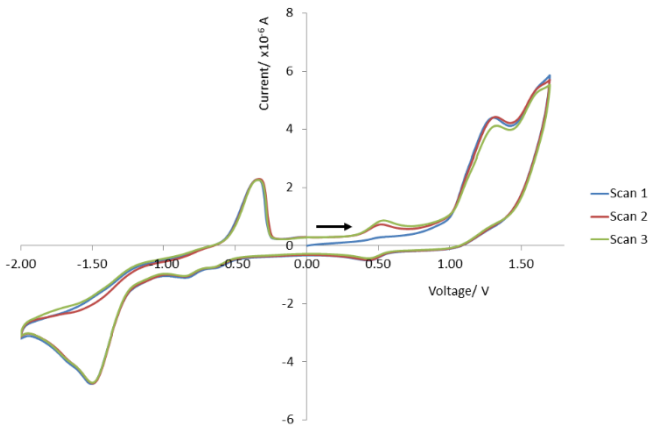
Cyclic voltammetry was conducted to probe the redox behaviour of the Cu(II) and Ni(II) complexes of **L**^{1}-**L**^{4} and the



ease that the phenolate moiety of **L**^{1} could be oxidised to form a phenoxyl radical.

Figure 7. Cyclic voltammograms of [Cu**L**^{2}]$^{2+}$, [Cu**L**^{3}]$^{2+}$ and [Cu**L**^{4}]$^{2+}$ at 0.2 V/s. Data collected in acetonitrile with tetrabutylammonium perchlorate as a supporting electrolyte at RT using a Ag/AgCl reference electrode.

Figure 7 shows the cyclic voltammograms for [Cu**L**^{2}]$^{2+}$, [Cu**L**^{3}]$^{2+}$ and [Cu**L**^{4}]$^{2+}$. The cyclic voltammograms for [Cu**L**^{2}]$^{2+}$, [Cu**L**^{3}]$^{2+}$ and [Cu**L**^{4}]$^{2+}$ compare well with those obtained by Camus *et. al.*,[78] who studied *C*- and *N*-functionalised cyclams to tune the coordination properties of the chelated copper(II). The irreversible copper(II) reduction to copper(I) is evidenced for all three complexes by the presence a wave at ~−0.8 V; the peak at ~−0.5 V is due to the same process for metallic copper. An oxidation peak at ~−0.15 V, characteristic of copper(0) to copper(II), is also observed. This irreversible peak, which is due to anodic stripping caused by the redissolution of metallic copper, is indicative of copper(0) formation due to dismutation of dissociated copper(II) ions.[79] Furthermore, this suggests that the electrogenerated copper(I) formed is unstable and dissociates during the timescale of the



electrochemical experiment. The anodic stripping process appears to be sensitive to the alkyl group at the phenolic site, in that the current intensity for this process is greatest for $[CuL^2]^{2+}$ and weakest for $[CuL^4]^{2+}$ i.e. $[CuL^2]^{2+} > [CuL^3]^{2+} > [CuL^4]^{2+}$

Figure 8. Consecutive cyclic voltammograms of $[CuL^1]^+$ at 0.2 V/s. Data collected in acetonitrile with tetrabutylammonium perchlorate as a supporting electrolyte at RT using a Ag/AgCl reference electrode.

Figure 8 shows the cyclic voltammagram of $[CuL^1]^+$. At +0.48 V a fully reversible peak is observed, which is assigned to the formation of the phenoxyl radical and subsequent reduction back to the phenolate. Reversibility of this wave was tested by plotting the peak current verses the square root of the scan rate. The resulting plot was linear; indicative of a reversible process. Previous work by Wieghardt and co-workers has been focused on the study of numerous metal complexes with phenolate pendent arms.[54] Their studies have shown that the redox potential for the phenoxyl radical/phenolate couple can vary depending on the metal centre. For a TACN (triazacyclononane) zinc(II) complex with a di-*tert*-butyl phenolate and two methyl pendent arms, the redox potential for the reversible formation of the phenoxyl radical is between −0.09 V and −0.32 V. When the methyl pendent arms are exchanged for acetates, values of 0.63, 0.73 and 0.36 V are obtained for the gallium(III), iron(III) and cobalt(III) metal complexes respectively.[22] One of us has also reported a cyclam-based ligand system analogous to L^1 (in terms of the pendent arm) that displays a single quasi-reversible peak at −0.58 V in the cyclic voltammogram.[80] The irreversible peak at +1.27 V is due to oxidation of an OH group, implying that the phenolate ligand has been protonated, and as such is not coordinated to the copper(II) centre. The difference in peak intensity between this peak and that of the phenoxyl radical suggests that the former is dominant. The appearance of the anodic region of the cyclic voltammaogram is very similar to that of those 7-, 8- and 9-hydroxy-3-ethoxycarbonyl-2,4-dimethyl coumarin[4,3-b] pyridine isomers studied by Pardo-Jiménez *et al*.[81]

The copper-based electrochemistry of $[CuL^1]^+$ is very similar to that of $[CuL^2]^{2+}$, $[CuL^3]^{2+}$ and $[CuL^4]^{2+}$. In the cathodic region the oxidation of copper(II) to copper(I) is again observed for the complex as well as metallic copper. Furthermore, anodic stripping is observed as an irreversible wave at −0.45 V.

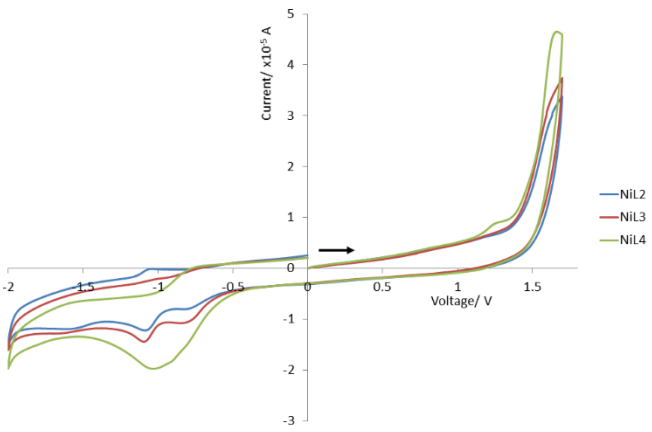


Figure 9. Cyclic voltammograms of $[NiL^2]^{2+}$, $[NiL^3]^{2+}$ and $[NiL^4]^{2+}$ recorded at 0.2 V/s. Data collected in acetonitrile with tetrabutylammonium perchlorate as a supporting electrolyte at RT using a Ag/AgCl reference electrode.

Figure 9 shows the cyclic voltammograms of the three nickel(II) complexes of $\mathbf{L^2}$, $\mathbf{L^3}$ and $\mathbf{L^4}$. The cyclic voltammogram of [Ni$\mathbf{L^4}$]$^{2+}$ differs considerably from [Ni$\mathbf{L^2}$]$^{2+}$ and [Ni$\mathbf{L^3}$]$^{2+}$, in that the nickel(II) to nickel(I) reduction for complexed and metallic nickel appears as a broad wave rather than two discrete waves in the cathodic region. In addition, it also displays a small irreversible oxidation wave at +1.22 V which is tentatively assigned to the Ni(II)/Ni(III) redox couple. Literature values for this process from other cyclam complexes vary between +1.07 and +1.52 V,[74] and +1.07 to +1.16 V.[77] [Ni$\mathbf{L^2}$]$^{2+}$ is the only complex to show some reversibility of the nickel(II) to nickel(I) reduction (wave at −1.1 V).

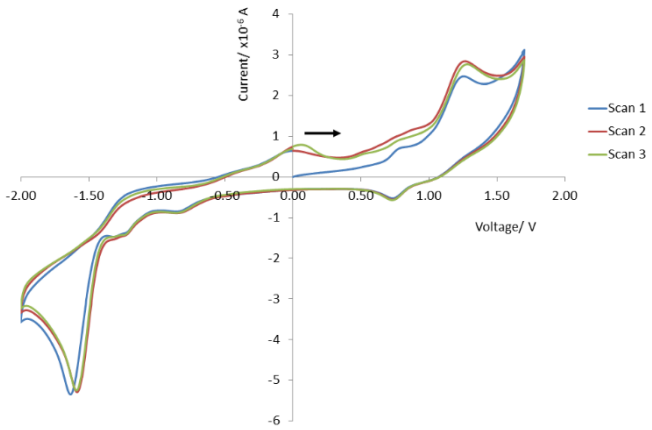


Figure 10. Consecutive cyclic voltammograms of [Ni$\mathbf{L_1}$]$^{+}$ 0.2 V/s. Data collected in acetonitrile with tetra-butyl ammonium perchlorate as a supporting electrolyte at RT using a Ag/AgCl reference electrode.

Figure 10 shows the cyclic voltammograms collected at a scan rate of 0.2 V/s for [Ni$\mathbf{L^1}$]$^{+}$. The reversible formation of the phenoxyl radical is observed at +0.74 V (reversibility of this wave was tested by plotting peak current verses the square root of scan rate; again a linear relationship ws observed). This is significantly more positive than for the copper(II) complex, meaning that the nickel(II) ion must be stabilising this redox process to a greater extent (i.e. a more positive potential is required to generate the radical species). Kimura and co-workers reported that the phenolate undergoes oxidation at +0.9 V at pH 10 for their nickel(II) complex of a cyclam ligand possessing a phenolate compared to +0.5 V uncoordinated.[21] The oxidative peak at +1.24 V is again due to the oxidation of the OH; this irreversible reduction is only 0.03 V different to the same electrochemical process when observed for [Cu$\mathbf{L^1}$]$^{+}$.

An interesting feature of the cyclic voltammogram arises in the second and third scans in that the initial oxidation of the phenolate to the phenoxyl radical is no longer clearly defined. Previously, nickel(II) complexes have been observed to possess two sets of quasi-reversible waves which are both part of the Ni(II)/Ni(III) process.[74,77] The relative size of these pairs of waves can vary considerably with the nature of the ligand, solvent and electrode. Oxidation potentials for the second set of waves occur between ~+0.5 to +1 V. It is, therefore, possible that a second set of waves for the Ni(II)/Ni(III) couple is formed after the initial scan near to the reversible wave of the phenoxyl radical. This may well lead to the distortion of the peak shape of the latter wave to the slope that is observed in scans two and three.

5. Conclusions

Side-bridged cyclam transition based metal complexes (M = Ni(II), Cu(II) and Zn(II)) bearing a phenolic ether or a phenolate pendent arm have been synthesised and characterised. UV-vis studies revealed that the identity of the phenolic ether had no effect on the geometry of the chelated metal ion. However, $[Cu\mathbf{L^1}]^+$ and $[Ni\mathbf{L^1}]^+$ showed significant differences in that the former was square-based pyramidal whilst the Ni(II) ion in the latter existed in either a square-planar or an octaedral geometry. For the Ni(II) and Cu(II) complexes of $\mathbf{L^1}$, evidence for a stable phenoxyl radical species is obtained (reversible peaks at +0.74 V and +0.48 V respectively), although evidence for the oxidation of OH, due to protonation of phenolate, is observed for both complexes at ~+1.24 V. The phenoxyl radical in $[Ni(\mathbf{L^1})]^{2+}$ complex is much harder to oxidise by 0.26 V compared to the analogous Cu(II) complex. The Ni(II) ion in the crystal structure of $[Ni(\mathbf{L^1})][(ClO_4)_2]$ possesses a distorted square-planar geometry in which the phenolic ether pendent arm is not involved in the coordination sphere. The cyclam ligand adopts a *trans*-II configuration. To our knowledge, this represents the first reported structural characterisation of a Ni(II) side-bridged cyclam complex.

Supporting Information CCDC 906943-909645 contain the supplementary crystallographic data for **3**, **11** and $[Ni\mathbf{L^2}]^{2+}$. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments REM wishes to thank the University of Hull for a studentship. SJA would like to thank the Daisy Appeal charity (grant no. DAhul2011) and for funding, and Dr Assem Allam and his family for the generous donation to help found the PET Research Centre at the University of Hull and for their continued support. We acknowledge the EPSRC UK National Mass Spectrometry Facility at Swansea University for the collection of mass spectrometry data.

Declarations of interest: none

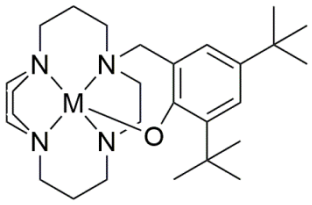
References

(1) Boswell, C. A.; Regino, C. A. S.; Baidoo, K. E.; Wong, K. J.; Bumb, A.; Xu, H.; Milenic, D. E.; Kelley, J. A.; Lai, C. C.; Brechbiel, M. W. *Bioconjugate Chem.* **2008**, *19*, 1476-1484.
(2) Boswell, C. A.; Sun, X.; Niu, W.; Weisman, G. R.; Wong, E. H.; Rheingold, A. L.; Anderson, C. J. *J. Med. Chem.* **2004**, *47*, 1465-1474.
(3) Burke, B. P.; Clemente, G. S.; Archibald, S. J. *J. Labelled Comp. Radiopharm.* **2014**, *57*, 239-243.
(4) Dale, A. V.; Il An, G.; Pandya, D. N.; Ha, Y. S.; Bhatt, N.; Soni, N.; Lee, H.; Ahn, H.; Sarkar, S.; Lee, W.; Huynh, P. T.; Kim, J. Y.; Gwon, M.-R.; Kirn, S. H.; Park, J. G.; Yoon, Y.-R.; Yoo, J. *Inorg. Chem.* **2015**, *54*, 8177-8186.
(5) Aung, W.; Jin, Z.-H.; Furukawa, T.; Claron, M.; Boturyn, D.; Sogawa, C.; Tsuji, A. B.; Wakizaka, H.; Fukumura, T.; Fujibayashi, Y.; Dumy, P.; Saga, T. *Molecular imaging* **2013**, *12*, 376-387.
(6) Gomes, A. J.; Espreafico, E. M.; Tfouni, E. *Mol. Pharmaceut.* **2013**, *10*, 3544-3554.
(7) Yu, M.; Lim, N. H.; Ellis, S.; Nagase, H.; Triccas, J. A.; Rutledge, P. J.; Todd, M. H. *Chemistryopen* **2013**, *2*, 99-105.
(8) Blahut, J.; Hermann, P.; Galisova, A.; Herynek, V.; Cisarova, I.; Tosner, Z.; Kotek, J. *Dalton Trans.* **2016**, *45*, 474-478.
(9) Fisher, C. M.; Fuller, E.; Burke, B. P.; Mogilireddy, V.; Pope, S. J. A.; Sparke, A. E.; Dechamps-Olivier, I.; Cadiou, C.; Chuburu, F.; Faulkner, S.; Archibald, S. J. *Dalton Trans.* **2014**, *43*, 9567-9578.
(10) Poty, S.; Gourni, E.; Desogere, P.; Boschetti, F.; Goze, C.; Maecke, H. R.; Denat, F. *Bioconjugate Chem.* **2016**, *27*, 752-761.
(11) Boros, E.; Holland, J. P.; Kenton, N.; Rotile, N.; Caravan, P. *ChemPlusChem* **2016**, *81*, 274-281.
(12) David, T.; Kubicek, V.; Gutten, O.; Lubal, P.; Kotek, J.; Pietzsch, H.-J.; Rulisek, L.; Hermann, P. *Inorg. Chem.* **2015**, *54*, 11751-11766.
(13) Halime, Z.; Frindel, M.; Camus, N.; Orain, P.-Y.; Lacombe, M.; Cherel, M.; Gestin, J.-F.; Faivre-Chauvet, A.; Tripier, R. *Org. Bio. Chem.* **2015**, *13*, 11302-11314.
(14) Burke, B. P.; Seemann, J.; Archibald, S. J. In *Advances in Inorganic Chemistry, Vol 68: Insights from Imaging in Bioinorganic Chemistry*, VanEldik, R.; Hubbard, C. D., Eds., 2016, pp 301-339.
(15) Liang, X.; Parkinson, J. A.; Weishäupl, M.; Gould, R. O.; Paisey, S. J.; Park, H.-s.; Hunter, T. M.; Blindauer, C. A.; Parsons, S.; Sadler, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 9105-9112.
(16) Khan, A.; Silversides, J. D.; Madden, L.; Greenman, J.; Archibald, S. J. *Chem. Commun.* **2006**, 416-418.
(17) Fricker, S. P. *Transfus. Med. Hemother.* **2013**, *40*, 237-245.
(18) Ross, A.; Choi, J.-H.; Hunter, T. M.; Pannecouque, C.; Moggach, S. A.; Parsons, S.; De Clercq, E.; Sadler, P. J. *Dalton Trans.* **2012**, *41*, 6408-6418.
(19) Poty, S.; Desogere, P.; Goze, C.; Boschetti, F.; D'Huys, T.; Schols, D.; Cawthorne, C.; Archibald, S. J.; Maecke, H. R.; Denat, F. *Dalton Trans.* **2015**, *44*, 5004-5016.
(20) Maples, R. D.; Cain, A. N.; Burke, B. P.; Silversides, J. D.; Mewis, R. E.; D'Huys, T.; Schols, D.; Linder, D. P.; Archibald, S. J.; Hubin, T. J. *Chem. Eur. J.* **2016**, *22*, 12916-12930.
(21) Iitaka, Y.; Koike, T.; Kimura, E. *Inorg. Chem.* **1986**, *25*, 402-404.
(22) Kimura, S.; Bill, E.; Bothe, E.; Weyhermüller, T.; Wieghardt, K. *J. Am. Chem. Soc.* **2001**, *123*, 6025-6039.
(23) Mewis, R. E.; Archibald, S. J. *Coord. Chem. Rev.* **2010**, *254*, 1686-1712.
(24) Chen, H.-H.; Yang, J.; Liu, Y.-Y.; Ma, J.-F. *CrystalEngComm* **2013**, *15*, 5168-5178.
(25) Matz, D. L.; Jones, D. G.; Roewe, K. D.; Gorbet, M.-J.; Zhang, Z.; Chen, Z.; Prior, T. J.; Archibald, S. J.; Yin, G.; Hubin, T. J. *Dalton Trans.* **2015**, *44*, 12210-12224.
(26) Wilson, K. R.; Cannon-Smith, D. J.; Burke, B. P.; Birdsong, O. C.; Archibald, S. J.; Hubin, T. J. *Polyhedron* **2016**, *114*, 118-127.
(27) Murray, B. S.; New, E. J.; Pal, R.; Parker, D. *Org. Bio. Chem.* **2008**, *6*, 2085-2094.
(28) Lau, Y. H.; Clegg, J. K.; Price, J. R.; Macquart, R. B.; Todd, M. H.; Rutledge, P. J. *Chem. Eur. J.* **2018**, *24*, 1573-1585.
(29) Wong, J. K. H.; Todd, M. H.; Rutledge, P. J. *Molecules* **2017**, *22*.
(30) Pujols-Ayala, I.; Barry, B. A. *Biochim. Biophys. Acta-Bioenerg.* **2004**, *1655*, 205-216.

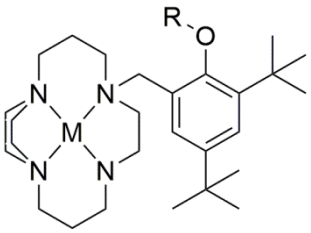
(31) Rogers, M. S.; Dooley, D. M. *Curr. Opin. Chem. Biol.* **2003**, *7*, 189-196.
(32) Auerbach, U.; Eckert, U.; Wieghardt, K.; Nuber, B.; Weiss, J. *Inorg. Chem.* **1990**, *29*, 938-944.
(33) Kimura, S.; Bill, E.; Bothe, E.; Weyhermüller, T.; Wieghardt, K. *J. Am. Chem. Soc.* **2001**, *123*, 6025-6039.
(34) Nirmala, G.; Rahiman, A. K.; Sreedaran, S.; Jegadeesh, R.; Raaman, N.; Narayanan, V. *Polyhedron* **2011**, *30*, 106-113.
(35) Moore, D. A.; Fanwick, P. E.; Welch, M. J. *Inorg. Chem.* **1989**, *28*, 1504-1506.
(36) Kimura, E. *Pure Appl. Chem.* **1986**, *58*, 1461-1466.
(37) Kimura, E.; Koike, T.; Takahasi, M. *J. Chem. Soc., Chem. Commun.* **1985**, 385-386.
(38) Kimura, E.; Koike, T.; Uenishi, K.; Davidson, R. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1110-1111.
(39) Kimura, E.; Koike, T.; Uenishi, K.; Hediger, M.; Kuramoto, M.; Joko, S.; Arai, Y.; Kodama, M.; Iitaka, Y. *Inorg. Chem.* **1987**, *26*, 2975-2983.
(40) Kimura, E.; Uenishi, K.; Koike, T.; Iitaka, Y. *Chem. Lett.* **1986**, 1137-1140.
(41) Maria, L.; Santos, I. C.; Alves, L. G.; Marçalo, J.; Martins, A. M. *J. Organomet. Chem.* **2013**, *728*, 57-67.
(42) Maria, L.; Santos, I. C.; Sousa, V. R.; Marçalo, J. *Inorg. Chem.* **2015**, *54*, 9115-9126.
(43) Bellouard, F.; Chuburu, F.; Kervarec, N.; Toupet, L.; Triki, S.; Le Mest, Y.; Handel, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3499-3505.
(44) J. Davies, P.; R. Taylor, M.; Wainwright, K. P. *Chem. Commun.* **1998**, 827-828.
(45) Royal, G.; Dahaoui-Gindrey, V.; Dahaoui, S.; Tabard, A.; Guilard, R.; Pullumbi, P.; Lecomte, C. *Eur. J. Org. Chem.* **1998**, *1998*, 1971-1975.
(46) Le Baccon, M.; Chuburu, F.; Toupet, L.; Handel, H.; Soibinet, M.; Dechamps-Olivier, I.; Barbiere, J. P.; Aplincourt, M. *New J. Chem.* **2001**, *25*, 1168-1174.
(47) Abdulwahaab, B. H.; Burke, B. P.; Domarkas, J.; Silversides, J. D.; Prior, T. J.; Archibald, S. J. *J. Org. Chem.* **2016**, *81*, 890-898.
(48) Silversides, J. D.; Burke, B. P.; Archibald, S. J. *Comptes Rendus Chimie* **2013**, *16*, 524-530.
(49) Boswell, C. A.; Regino, C. A. S.; Baidoo, K. E.; Wong, K. J.; Milenic, D. E.; Kelley, J. A.; Lai, C. C.; Brechbiel, M. W. *Biorg. Med. Chem.* **2009**, *17*, 548-552.
(50) Smith, R.; Huskens, D.; Daelemans, D.; Mewis, R. E.; Garcia, C. D.; Cain, A. N.; Freeman, T. N. C.; Pannecouque, C.; De Clercq, E.; Schols, D.; Hubin, T. J.; Archibald, S. J. *Dalton Trans.* **2012**, *41*, 11369-11377.
(51) Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112-122.
(52) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837-838.
(53) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
(54) Sokolowski, A.; Müller, J.; Weyhermüller, T.; Schnepf, R.; Hildebrandt, P.; Hildenbrand, K.; Bothe, E.; Wieghardt, K. *J. Am. Chem. Soc.* **1997**, *119*, 8889-8900.
(55) Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833-7863.
(56) Counsell, R. E.; Desai, P.; Kulkarni, P. G. *J. Med. Chem.* **1971**, *14*, 789-792.
(57) Jiménez, C. A.; Belmar, J. B. *Tetrahedron* **2005**, *61*, 3933-3938.
(58) Hansen, M. H.; Riggs, J. R. *Tetrahedron Lett.* **1998**, *39*, 2705-2706.
(59) Stockheim, C.; Hoster, L.; Weyhermüller, T.; Wieghardt, K.; Nuber, B. *J. Chem. Soc., Dalton Trans.* **1996**, 4409-4416.
(60) Le Baccon, M.; Chuburu, F.; Toupet, L.; Handel, H.; Soibinet, M.; Dechamps-Olivier, I.; Barbier, J.-P.; Aplincourt, M. *New J. Chem.* **2001**, *25*.
(61) McOmie, J. F. W.; West, D. E. *Organic Synthetic Collection* **1973**, *5*, 412-414.
(62) Vankar, Y. D.; Rao, C. T. *J. Chem. Res., Synop* . **1985**, 232-233.
(63) Binkley, R. W.; Hehemann, D. G. *J. Org. Chem.* **1990**, *55*, 378-380.
(64) Riley, J. G.; Grindley, T. B. *J. Carbohydr. Chem.* **2001**, *20*, 159-169.
(65) Petchmanee, T.; Ploypradith, P.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 2892-2895.
(66) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477-5478.
(67) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823-3824.

(68) Lesk, A.; Nudelman, A. *Synth. Commun.* **1999**, *29*, 1405-1408.
(69) Hodgetts, K. J.; Wallace, T. W. *Synth. Commun.* **1994**, *24*, 1151-1155.
(70) Cappa, A.; Marcantoni, E.; Torregiani, E. *J. Org. Chem.* **1999**, *64*, 5696-5699.
(71) Hampton, C. S.; Harmata, M. *Tetrahedron* **2016**, *72*, 6064-6077.
(72) Bosnich, B.; Poon, C. K.; Tobe, M. L. *Inorg. Chem.* **1965**, *4*, 1102-1108.
(73) Thom, V. J.; Fox, C. C.; Boeyens, J. C. A.; Hancock, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 5947-5955.
(74) Dong, Y.; Lawrence, G. A.; Lindoy, L. F.; Turner, P. *Dalton Trans.* **2003**, 1567-1576.
(75) Fabbrizzi, L.; Montagna, A.; Poggi, A.; Kaden, T. A.; Siegfried, L. C. *Dalton Trans.* **1987**, 2631-2634.
(76) Silversides, J. D.; Allan, C. C.; Archibald, S. J. *Dalton Trans.* **2007**, 971-978.
(77) Dong, Y.; Lindoy, L. F.; Turner, P.; Wei, G. *Dalton Trans.* **2004**, 1264-1270.
(78) Camus, N.; Le Bris, N.; Nuryyeva, S.; Chessé, M.; Esteban-Gómez, D.; Platas-Iglesias, C.; Tripier, R.; Elhabiri, M. *Dalton Trans.* **2017**, *46*, 11479-11490.
(79) Grujicic, D.; Pesic, B. *Electrochim. Acta* **2002**, *47*, 2901-2912.
(80) Aranburu Leiva, A.; Kaur, M.; Benjamin, S.; Jones, A.; Langley, S.; Mewis, R. *Molbank* **2017**, *2017*, M963.
(81) Pardo-Jiménez, V.; Barrientos, C.; Squella, J. A.; Navarrete-Encina, P. A.; Nuñez-Vergara, L. J. *J. Electrochem. Soc.* **2011**, *158*, F166-F172.

Side-bridged cyclam complexes bearing a phenolic ether or phenolate pendent arm were synthesised. The oxidation potential of the $Cu^{I/II}$ redox couple changed in the order *p*-methoxybenzyl≈H<benzyl<methyl. For $[Ni\mathbf{L^1}]^+$ and $[Cu\mathbf{L^1}]^+$, evidence for a phenoxyl radical was obtained (quasi reversible peak at +0.74 V and +0.48 V respectively).



M**L**^{1}



M**L**^{2} R = Me
M**L**^{3} R = Bn
M**L**^{4} R = *p*-OMeBn