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The structural and electrochemical consequences of hydrogenating copper N₂S₂ Schiff base macrocycles

Katherine D. Trotter^a, Michelle K. Taylor^a, John C. Forgie^a, John Reglinski^{a,*}, Leonard E.A. Berlouis^a, Alan R. Kennedy^a, Corinne M. Spickett^b, Rebecca J. Sowden^b

^a Department of Pure and Applied Chemistry, 295 Cathedral St., Strathclyde University, Glasgow G1, 1XL, United Kingdom ^b Strathclyde Institute of Pharmacy and Biomedical Sciences, 27 Taylor Street, Strathclyde University, Glasgow G4 0NR, United Kingdom

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ABSTRACT

A series of *cis* and *trans* tetradentate copper macrocyclic complexes, of ring size 14–16, that employ amine and thioether donor groups are reported. Apart from 5,6,15,16-bisbenzo-8,13-diaza-1,4-dithia-cyclohexadecane copper(I) (*cis*-[Cu(H₄N_{bu}S_{en})]⁺) all of the complexes are obtained in the copper(II) form. Crystallographic analysis shows that the copper(II) complexes all adopt a distorted planar geometry around the copper. In contrast, *cis*-[Cu(H₄N_{bu}S_{en})]⁺ is found to adopt a distorted tetrahedral geometry. The complexes were subjected to electrochemical analysis in water and acetonitrile. The effect of the solvent, positions of the donor atoms (*cis*/*trans*) on $E^{1/2}$ is discussed as is the comparison of the electrochemical behaviour of these complexes with their parent Schiff base macrocycles.

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1. Introduction

Copper macrocycles are of considerable interest as low molecular weight models of biological copper-containing redox proteins. There have been numerous reports of the synthesis of copper macrocycles, including ones with tetradentate N₄ or S₄ ligands, and their geometrical and electrochemical properties [1]. Comparative studies of ligands with mixed thioether and amine donors have also been carried out [2,3]. Ligands with an N₂S₂ donor set are better models for biological copper centres as they increase the stability of copper in the divalent form, facilitating redox reactions at the metal centre [2–5]. However, there have been few systematic studies of the relationships between ring size, complex stability, and electrochemical potential in such systems.

We are interested in developing copper-based redox sensors for the detection of reactive oxygen species in biological systems, which requires metal complexes that are stable in both the monovalent and divalent forms, and have a redox potential in the range 0.2–0.8 V. Preliminary work with symmetric, salicylidene based N₂S₂ Schiff base copper complexes with ethylene, propylene or butylene donor spacers suggested that it would be feasible to obtain complexes with the requisite redox properties [4,5]. However, these open tetradentate N_2S_2 Schiff base ligands (Fig. 1, 1) were found to undergo partial hydrolysis and dissociation of the metal on oxidation by biologically-relevant oxidants [5,6]. Consequently, the corresponding Schiff base macrocycles were synthesized; these compounds were more resistant to hydrolysis, but their general water solubility was still poor [6,7]. Furthermore, although these divalent copper complexes can be stoichiometrically reduced by biologically relevant species, their re-oxidation led to significant degradation in the organic portion of the compound [6]. On the positive side, there was no evidence of redox cycling by reaction with molecular oxygen (Eq. (1)), as it was possible to reduce them quantitatively with a range of reducing agents in the presence of oxygen [6]. This is important, as quantitative measurement of oxidant production and biological redox balance requires that the redox sensor should not undergo cycling of the kind observed with many simple copper (and other transition metal) complexes [8,9] (Eq. (1)). Thus copper macrocycles of the generic structure shown in Fig. 1 (2) have potential as redox sensors, if they can be stabilized against hydrolysis on chemical oxidation.







^{*} Corresponding author. Tel.: +44 0141 548 2349; fax: +44 0141 548 4822. *E-mail address:* j.reglinski@strath.ac.uk (J. Reglinski).

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Fig. 1. The design of copper redox-sensing agents: copper Schiff base (a), copper Schiff base macrocycles (b) and copper amine macrocycles (c) [6,7]. Families of complexes can be generated by altering the number of methylene units $((-CH_2-)n, n = 2, 3)$ between the donor atoms. Charges and oxidation states are omitted as individual species can exist in either of both forms.

Mass spectrometry data suggested that the copper Schiff base macrocycles were prone to oxidation at the imine groups [6] and it was decided to hydrogenate them, thus converting the Schiff base macrocycles (Fig. 1, 2) into amine macrocycles (Fig. 1, 3). The synthesis and structure of one of these copper complexes, with ethylene bridges between both pairs of donor atoms (Fig. 1), has previously been reported by Bentfield et al. [10]. Importantly, they were able to isolate both forms of the complex, i.e. Cu(I) and Cu(II), and their electrochemical analysis suggests that, similar to the Schiff base complexes [3], it would be possible to oxidise this species reversibly with chemical oxidants. Complexes of the same ligands, but with nickel as the metal, have also been synthesized and their stability investigated previously [11]. However, as yet a systematic study of the effect of ring size and geometry on the electrochemical properties of the copper macrocycle family shown in Fig. 1 (3) has not been reported. These macrocycles should have important advantages for biological applications over some of those described previously [2,3], in terms of their electrochemical properties and resistance to loss of the metal ion. Hence the aim of this work was to synthesize a small family of cis and trans amine-thioether copper macrocycles with differing ring sizes and geometries, and investigate their aqueous stability and electrochemical properties.

2. Experimental

Unless otherwise stated all chemicals were commercially obtained and used without further purification. The Schiff base macrocycles and cis- $[Ni(H_4N_{pr}S_{en})Cl(OH_2)]^+$ are prepared as previously reported [6,7,11,12]. Solvents were used as supplied, apart from the acetonitrile, which was re-distilled over calcium hydride prior to its use in the electrochemical studies. All NMR spectra were recorded on either a Bruker DPX400 or a Bruker AV500. The spectra were referenced to internal solvent peaks and thus to TMS. Solid reflectance spectra (400–900 nm) were recorded on a Photonics CCD array UV–Vis spectrophotometer. Mass spectra were recorded using a Thermo Finnigan LCQDuo by electrospray ion trap.

Crystals were coated in mineral oil and mounted on glass fibres. Data were collected at 123 K on a Nonius Kappa CCD diffractometer using graphite monochromated Mo K α radiation. The heavy atom positions were determined by Patterson methods and the remaining atoms located in the difference electron density maps. Full matrix least squares refinement was based on F_2 with all non-hydrogen atoms anisotropic. While the hydrogen atoms were mostly observed in the difference maps, they were placed in calculated positions riding on the parent atoms. The positions of the protons on the coordinated water in *cis*-[Cu^{II}(H₄N_{pr}S_{pr})(OH₂)]²⁺ were calculated using CALC-OH [13]. The structure solution and refinement used the programs SHELX-97 [14] or SIR 92 [15] and the graphical interface WINGX [16]. A summary of the crystallographic parameters are given in Table 1.

Cyclic voltammetry in aqueous solution was carried out on a CH Instruments 660A Electrochemical Workstation with iR compensation, using ultra high purity water (Elga: 0.22μ filtered, 17 M Ω /cm) and acetonitrile (redistilled from calcium hydride). The electrodes

were glassy carbon, platinum wire and silver wire as the working, counter and reference electrodes, respectively. All solutions were degassed with argon and contained sample concentrations 2×10^{-3} M for water and 4×10^{-3} M for acetonitrile, together with the supporting electrolyte; NaCl (0.1 M) and ^tBu₄NBF₄ (0.1 M), respectively. Measurements in aqueous and non-aqueous solution were referenced against the redox couples ($E^{1/2}$) of potassium ferricyanide/ferrocyanide and ferrocene/ferrocenium, respectively. This allowed for the data to be referred back to silver wire, which is the common reference electrode for both series of experiments.

2.1. Preparation of cis-amine macrocycles

Briefly 4.5 g (excess) NaBH₄ was added to a stirred solution of 0.66 mmol of the relevant Schiff base macrocycle in 500 ml ethanol in small portions over approximately 1 h, upon which the solution became pale yellow. The reaction mixture was cooled in an ice bath and kept under a N₂ blanket during addition of NaBH₄ for safety. The solvent was removed and 100 ml distilled water added. The product was then extracted into 3×200 ml chloroform. The extracts were combined, washed with 100 ml distilled water and dried over anhydrous sodium sulphate. The solution was filtered and the solvent removed to give yellow oils apart from *cis*-H₄N_{bu}S_{bu} which was obtained as a white mass. Typical yields of 80% were obtained.

2.1.1. cis-H₄N_{en}S_{en}

¹H NMR (400 MHz, CDCl₃; $\delta_{\rm H}$) 7.39 (m, 2H, arom), 7.29 (m, 2H, arom), 7.18 (m, 4H, arom), 3.81 (s, 4H, –CH₂–), 3.27 (s, 4H, –SCH₂–), 2.92 (s, 4H, –NCH₂). ¹³C NMR (100 MHz, CDCl₃; $\delta_{\rm C}$) 141, 134, 131, 130, 128, 127 (arom), 52 (–CH₂–), 48 (–SCH₂–), 34 (–NCH₂–). Mass spec. (ESI) *m/z* 331 [MH]⁺.

2.1.2. $cis-H_4N_{pr}S_{en}$

¹H NMR (400 MHz, CDCl₃; $\delta_{\rm H}$) 7.55 (d, 2H, arom), 7.26 (m, 2H, arom), 7.18 (d, 4H, arom), 4.16 (s, 4H, $-\rm CH_2-$), 3.36 (s, 4H, $-\rm SCH_2-$), 2.94 (t, 4H, $-\rm NCH_2$), 2.07 (p, 2H, $-\rm NCH_2\rm CH_2-$). ¹³C NMR (100 MHz, CDCl₃; $\delta_{\rm C}$) 136, 134, 133, 131, 128, 127 (arom), 54 ($-\rm CH_2-$), 49 ($-\rm SCH_2-$), 33 ($-\rm NCH_2-$), 19 ($-\rm NCH_2\rm CH_2-$). Mass spec. (ESI) m/z 345 [MH]⁺.

2.1.3. $cis-H_4N_{bu}S_{en}$

¹H NMR (400 MHz, CDCl₃; $\delta_{\rm H}$) 7.40 (m, 4H, arom), 7.23 (m, 4H, arom), 3.95 (s, 4H, –CH₂–), 3.27 (s, 4H, –SCH₂–), 2.73 (t, 4H, –NCH₂), 1.73 (m, 4H, –NCH₂CH₂–). ¹³C NMR (100 MHz, CDCl₃; $\delta_{\rm C}$) 134, 132, 131, 129, 128, 127.5 (arom), 48 (–SCH₂–), 34 (–NCH₂–), 27 (–NCH₂CH₂–). Mass spec. (ESI) *m/z* 359 [MH]⁺.

2.1.4. cis-H₄N_{en}S_{pr}

¹H NMR (400 MHz, CDCl₃; $\delta_{\rm H}$) 7.53 (d, 2H, arom), 7.36 (d, 2H, arom), 7.18 (m, 4H, arom), 3.83 (s, 4H, $-CH_2-$), 3.18 (t, 4H, $-SCH_2-$), 2.79 (s, 4H, $-NCH_2$), 1.85 (p, 2H, $-SCH_2CH_2-$). $\delta_{\rm C}$ (100 MHz; solvent CDCl₃) 141, 135, 132, 131, 128, 127 (arom), 53 ($-CH_2-$), 49 ($-SCH_2-$), 35 ($-NCH_2-$), 28 ($-SCH_2CH_2-$). Mass spec. (ESI) *m*/*z* 345 [MH]⁺.

Table 1

Crystallographic details. Problems were encountered with the $[BF_4]^-$ anions associated with cis- $[Cu(H_4N_{bu}S_{en})]^+$ which influenced the refinement process. This is discussed further in the supplementary material where a view of the extend structure is given.

	cis-[Cu(H ₄ N _{pr} S _{en})] (BF ₄) ₂	cis-[Cu(H ₄ N _{pr} S _{pr})OH ₂] (BF ₄) ₂	cis-[Cu(H ₄ N _{bu} S _{en})] BF ₄	cis-[Cu(H ₄ N _{en} S _{pr})] (BF ₄) ₂
Empirical formula	C ₁₉ H ₂₄ B ₂ CuF ₈ N ₂ S ₂	C ₂₀ H ₂₈ B ₂ CuF ₈ N ₂ OS ₂	$C_{20}H_{26}BCuF_4N_2S_2$	$C_{19}H_{24}B_2CuF_8N_2S_2$
FW	581.68	613.7	500.76	584.1
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	P21/c	P21/n	C2/c	P21/c
a (Å)	8.3990(8)	14.1716(7)	25.6592(10)	12.7779(4)
b (Å)	17.1050(17)	11.5191(5)	16.7535(7)	20.5576(7)
c (Å)	15.5630(15)	15.6357(10)	16.3163(4)	19.0148(6)
α (°)	92.425(3)	105.621(6)	91.221(3)	108.178(2)
β (°)				
γ (°)				
Z	4	4	12	8
$V(\dot{A}^3)$	2233.94(5)	2458.2(2)	7012.5(4)	4745.6(3)
$\mu_{calc} (mm^{-1})$	1.243	1.137	1.151	1.172
Number of refections measured	9804	23,331	21,486	21,367
Number of unique refections	5036	6092	6149	10,882
No. observed	3832	3666	4621	4780
No. parameters	307	339	438	621
$R (I > 2\sigma(I))$	0.0574	0.0457	0.0609	0.0699
wR2 (all reflns)	0.1571	0.1095	0.0913	0.1740
Goodness-of-fit	1.164	0.926	1.109	1.023
	cis-[Ni(H ₄ N _{pr} S _{en})Cl(OH ₂)] BF ₄	cis-[Cu(H ₄ N _{pr} S _{en})Cl] BF ₄	$[CuCl_2(cis-H_6N_{bu}S_{pr})_2] (PF_6)_2$	$H_6N_{pr}S_{bu}$ (BF ₄) ₂
Empirical formula	C19H26BCIF4N2NiOS2	C ₁₉ H ₂₄ BClCuF ₄ N ₂ S ₂	C44H66Cl2CuF12N4O2 P2S4	$C_{21}H_{30}B_2F_8N_2S_2$
FW	543.51	530.32	1235.63	548.21
Crystal system	triclinic	monoclinic	triclinic	monoclinic
Space group	ΡĪ	P21/a	ΡĪ	C2/c
a (Å)	8.3859(10)	8.392(12)	8.2322(9)	17.1185(10)
b (Å)	10.9303(13)	19.206(12)	10.2439(11)	10.0403(6)
c (Å)	13.3650(15)	13.12(2)	16.1675(17)	16.0010(10)
α (°)	111.698(2)	92.07(13)	86.941(2)	118.358(3)
β (°)	99.918(2)		76.566(2)	
γ (°)	92.152(2)		85.969(2)	
Ζ	2	2	1	4
$V(Å^3)$	1114.4(2)	2113(5)	1321.9(2)	2420.13(3)
$\mu_{calc} (mm^{-1})$	1.226	1.402	0.816	0.296
Number of refections measured	13,065	19,363	12,432	4882
Number of unique refections	6616	4868	6420	2623
No observed	4991	3169	4400	1609
No. parameters	384	339	335	159
$R(I > 2\sigma(I))$	0.042	0.0945	0.0555	0.0488
wR2 (all refins)				
ma (an renno)	0.1273	0.2541	0.1523	0.1125

2.1.5. cis-H₄N_{pr}S_{pr}

¹H NMR (400 MHz, CDCl₃; $\delta_{\rm H}$) 7.42 (d, 2H, arom), 7.31 (d, 2H, arom), 7.19 (m, 4H, arom), 3.94 (s, 4H, $-CH_2-$), 3.05 (t, 4H, $-SCH_2-$), 2.77 (t, 4H, $-NCH_2$), 1.97 (p, 2H, $-SCH_2CH_2-$), 1.82 (s, br, 2H, NH), 1.72 (p, 2H, $-NCH_2CH_2-$). ¹³C NMR (100 MHz, CDCl₃; $\delta_{\rm C}$) 141, 135, 131, 130, 128, 127 (arom), 52 ($-CH_2-$), 48 ($-SCH_2-$), 34 ($-NCH_2-$), 30 ($-SCH_2CH_2-$), 29 ($-NCH_2CH_2-$). Mass spec. (ESI) *m*/*z* 359 [MH]⁺.

2.1.6. $cis-H_4N_{bu}S_{pr}$

¹H NMR (400 MHz, CDCl₃; $\delta_{\rm H}$) 7.38 (d, 2H, arom), 7.29 (d, 2H, arom), 7.19 (m, 4H, arom), 3.90 (s, 4H, –CH₂–), 3.09 (t, 4H, –SCH₂–), 2.62 (t, 4H, –NCH₂), 2.06 (p, 2H, –SCH₂CH₂–), 1.57 (p, 4H, –NCH₂CH₂–). ¹³C NMR (100 MHz, CDCl₃; $\delta_{\rm C}$) 141, 135, 131, 130, 129, 127 (arom), 52 (–CH₂–), 48 (–SCH₂–), 34 (–NCH₂–), 29 (–SCH₂CH₂–), 27 (–NCH₂CH₂–). Mass spec. (ESI) *m/z* 373 [MH]⁺.

2.1.7. cis-H₄N_{en}S_{bu}

¹H NMR (500 MHz, CDCl₃; $\delta_{\rm H}$) 7.37 (d, 2H, arom), 7.30 (d, 2H, arom), 7.20 (t, 2H, arom), 7.15 (t, 2H, arom) 3.89 (s, 4H, -CH₂-), 2.93 (t, 4H, -SCH₂), 2.89 (s, 4H, -NCH₂-), 1.74 (p, 4H, -SCH₂CH₂-). ¹³C NMR (125 MHz, CDCl₃; $\delta_{\rm C}$) 141, 135, 131, 130, 128, 127 (arom), 53 (-CH₂-), 49 (-SCH₂-), 34 (-NCH₂-), 28 (-SCH₂CH₂-). Mass spec. (ESI) *m/z* 359.

2.1.8. $cis-H_4N_{pr}S_{bu}$

¹H NMR (500 MHz, CDCl₃; $\delta_{\rm H}$) 7.33 (d, 2H, arom), 7.31 (d, 2H, arom), 7.20 (t, 2H, arom), 7.15 (t, 2H, arom) 3.91 (s, 4H, -CH₂-), 2.96 (t, 4H, -SCH₂), 2.70 (t, 4H, -NCH₂-), 1.78 (m, 6H, -SCH₂CH₂-, -NCH₂CH₂-,). ¹³C NMR (125 MHz, CDCl₃; $\delta_{\rm C}$) 140, 135, 130, 129, 128, 126 (arom), 52 (-CH₂-), 47 (-SCH₂-), 34 (-NCH₂-), 30 (-SCH₂CH₂-), 28 (-NCH₂CH₂-). Mass spec. (ESI) *m*/*z* 373.

2.1.9. cis- $H_4N_{bu}S_{bu}$

¹H NMR (500 MHz, CDCl₃; $\delta_{\rm H}$) 7.34 (m, 4H, arom), 7.21 (m, 4H, arom), 4.78 (s, 1H, -NH-), 4.56 (s, 1H, -NH-), 4.00 (m, 2H, -PhCH₂N-), 3.82 (m, 2H, -PhCH₂N-), 3.07, (m, 4H, NCH₂-), 2.72 (m, 4H, SCH₂-), 1.85 (m, 4H, SCH₂CH₂), 1.71 (m, 4H, SCH₂CH₂). ¹³C NMR (125 MHz, CDCl₃; $\delta_{\rm C}$) 135 (×2), 133 (×2) 132 (×2), 130 (×2) 129 (×2), 126 (×2) (all arom), 60 (N-CH₂), 55 (N-CH₂-CH₂), 33 (S-CH₂), 28 (N-CH₂-CH₂), 24 (S-CH₂-CH₂) Proton assignments are made using 2D [¹H, ¹H] COSY and 2D [¹H, ¹³C] HSQC NMR spectra.^ξ Mass spec. (ESI) *m/z* 387 [MH]⁺.

2.2. Preparation of trans-amine macrocycles

Briefly, 0.2 g (5.3 mmol) LiAlH₄ was added under a blanket of N_2 to a cooled (4 °C), stirred solution of 2.66 mmol of the relevant Schiff base macrocycle in 75 ml THF in small portions over approximately 1 h. The reaction mixture was stirred overnight under a N_2

blanket after which time the reaction was quenched by the dropwise addition of water (0.2 ml), 20% potassium hydroxide solution (0.2 ml) and water (0.6 ml). The solution was filtered and the solvent removed leaving an oil which was used without further purification. Typical yield 70%.

2.2.1. trans- $H_4(N-en-S)_2$

¹H NMR (400 MHz, CDCl₃; $\delta_{\rm H}$) 7.45 (m, 8H, arom), 3.72 (s, 4H, –PhCH₂N–), 3.22, (t, 4H, NCH₂–), 2.89 (t, 4H, SCH₂–). Mass spec. (ESI) *m*/*z* 331 [MH]⁺.

2.2.2. trans-H₄(N-pr-S)₂

¹H NMR (400 MHz, CDCl₃; δ_{H}) 7.20 (m, 8H, arom), 3.94 (s, 4H, –PhCH₂N–), 3.04, (t, 4H, NCH₂–), 2.82 (t, 4H, SCH₂–), 1.93 (q, 4H, –CH₂–). Mass spec. (ESI) *m/z* 359 [MH]⁺.

2.3. Preparation of cis-[Cu(II)H₄N_{en}S_{en}] (BF₄)₂ [10]

Cu(BF₄)₂·H₂O (0.24 g, 1 mmol) in methanol (5 ml) was added dropwise to a solution of H₄N_{en}S_{en} (0.35 g, 1 mmol) in methanol (20 ml). The solution, which turned dark green, was refluxed for 1 h and hot filtered. The solvent was removed to give a dark green solid. The solid was redissolved in the minimum amount of methanol, filtered through Celite and recrystallised by vapour diffusion with diethyl-ether to give a dark green crystalline material. *Anal.* Calc. for C₁₈H₂₂N₂B₂CuF₈S₂: C, 38.09; H, 3.91; N, 4.94. Found: C, 38.00; H, 4.04; N, 4.45%. Mass spec. (ESI) *m*/*z* 196.5, 393 [MH²⁺], [MH⁺]. λ_{max} = 425 nm, 560 nm.

2.4. Preparation of cis-[Cu(II)H₄N_{en}S_{pr}] (BF₄)₂

Cu(BF₄)₂·H₂O (0.07 g, 0.29 mmol) in methanol (5 ml) was added dropwise to a solution of H₄N_{en}S_{pr} (0.1 g, 0.29 mmol) in methanol (10 ml). The dark green/brown solution was refluxed for 1 h, hot filtered and cooled. The dark green brown solution was filtered through Celite and recrystallised by vapour diffusion with diethyl-ether to give dark green crystals suitable for X-ray analysis. *Anal.* Calc. for C₁₉H₂₄N₂S₂CuB₂F₈: C, 39.23; H, 4.16; N, 4.82. Found: C, 39.68; H, 4.33; N, 4.75%. Mass spec. (ESI) *m/z* 407 [MH⁺]. λ_{max} = 415 nm.

2.5. Preparation of cis-[Cu(II)H₄N_{en}S_{bu}] (BF₄)₂

Cu(BF₄)₂·H₂O (0.07 g, 0.29 mmol) in methanol (5 ml) was added dropwise to a solution of H₄N_{en}S_{bu} (0.1 g, 0.29 mmol) in methanol (50 ml). The solution was refluxed for 1 h allowed to cool and then filtered. The solvent was removed under pressure and the brown residue extracted with methanol. The product was crystallised directly from this solution by vapour diffusion with diethyl-ether to give dark green crystals which were unsuitable for X-ray analysis. *Anal.* Calc. for C₂₀H₂₆N₂S₂CuB₂F₈·1H₂O: C, 39.14; H, 4.49; N, 4.56. Found: C, 39.24; H, 4.74; N, 4.84%. Mass spec. (ESI) *m/z* 421 [MH⁺]. λ_{max} = 455 nm.

2.6. Preparation of cis-[Cu(II)H₄N_{pr}S_{en}] $(BF_4)_2$

Cu(BF₄)₂·H₂O (0.24 g, 1 mmol) in methanol (5 ml) was added dropwise to a solution of H₄N_{pr}S_{en} (0.35 g, 1 mmol) in methanol (20 ml). The solution, which turned dark green, was refluxed for 1 h and hot filtered. The solvent was removed to give a dark green solid. The solid was redissolved in the minimum amount of methanol, filtered through Celite and recrystallised by vapour diffusion with diethyl-ether to give dark green crystals suitable for X-ray analysis. *Anal.* Calc. for C₁₉H₂₄N₂B₂CuF₈S₂: C, 39.23; H, 4.16; N, 4.82. Found: C, 39.82; H, 3.78; N, 4.50%. Mass spec. (ESI) *m*/*z* 407 [MH⁺]. λ_{max} = 430 nm, 580 nm.

2.7. Preparation of cis-[Cu(II)H₄N_{pr}S_{pr}] (BF₄)₂

Cu(BF₄)₂·H₂O (0.067 g, 0.28 mmol) in methanol (5 ml) was added dropwise to a solution of $H_4N_{pr}S_{pr}$ (0.1 g, 0.28 mmol) in methanol (10 ml). The dark green solution was refluxed for 1 h, hot filtered and cooled. The dark green brown solution was then filtered through Celite and recrystallised by vapour diffusion with diethyl-ether to give dark green crystals suitable for X-ray analysis. The structure shows that the resulting complex contains a coordinated water molecule. *Anal.* Calc. for C₂₀H₂₈N₂B₂CuF₈OS₂: C, 39.14; H, 4.60; N, 4.56%, Calc. for C₂₀H₂₆N₂S₂Cu.B₂F₈: C, 40.32; H, 4.40; N, 4.70%. Found: C, 40.14; H, 4.29; N, 4.52%. Mass spec (ESI) *m/z* 421 [MH⁺]. λ_{max} = 440 nm, 570 nm.

2.8. Preparation of cis-[Cu(I)H₄N_{bu}S_{en}] BF_4

Cu(BF₄)₂·H₂O (0.24 g, 1 mmol) was added to a solution of H₄N_{bu}S_{en} (0.35 g, 1 mmol) in chloroform (20 ml). The mixture was placed in an ultrasonic bath (5 min) to disperse the copper salt. The resulting yellow mixture was refluxed for 2 h and then hot filtered. The solvent was removed to give a pale vellow solid, which was dissolved in the minimum amount of acetonitrile and recrystallised by vapour diffusion with diethyl-ether. Anal. Calc. for C₂₀H₂₆N₂BCuF₄S₂·2H₂O: C, 44.08 ; H, 5.55; N, 5.14. Found: C, 44.12; H, 5.16; N, 5.14%. ¹H NMR (400 MHz, DCM; $\delta_{\rm H}$) 7.47–7.39 (m, 4H, arom), 7.34-7.29 (m, 4H, arom), 4.10, (t, 2H, SCH_a), 3.95, (d, 2H, -CH_aN-), 3.69, (d, 2H, -SCH_b-), 3.42 (MeOH), 3.39, (t, 2H, NCH_a), 2.99, (br d, 4H, NCH_b and NH) 2.73 (t, 2H, -CH_bN-), 2.17, (p, 2H, -NCH₂CH_a), 1.86, (q, 2H, -NCH₂CH_b-). ¹³C NMR (100 MHz, DCM; $\delta_{\rm C}$) 137, 133, 131, 129, 128, 127 (arom), 56 (-SCH₂-) 48 (-NCH₂-), 33 (-CH₂N-), 25 (-NCH₂CH₂-). Mass spec. (ESI) m/z 421 [MH⁺].

2.9. Preparation of $[CuCl_2(cis-H_6N_{bu}S_{pr})_2]$ (PF₆)₂

Cu(MeCN)₄ PF₆ (0.100 g, 0.27 mmol) was treated with H₄N_{bu}S_{pr} (0.100 g, 0.27 mmol) in methanol (50 ml). The solution was refluxed for 2 h. The solution was allowed and the solvent removed. The yellow oil was crystallised from methanol/diethyl-ether by vapour diffusion. After a prolonged period a few crystals formed which were identified crystallographically as $[CuCl_2(cis-H_4N_{bu}S_{pr})_2]^{2+}$ 2PF₆.

2.10. Preparation of trans-[Cu(II)H₄(N_2S_2)] (BF₄)₂

 $Cu(BF_4)_2 \cdot H_2O(0.25 \text{ g}, 0.8 \text{ mmol})$ in methanol (10 ml) was added to a solution of the relevant *trans*-H₄(N₂S₂) macrocycle (0.26 g, ~0.8 mmol) in methanol (40 ml). The solution was refluxed for 3 h and then allowed to cool. The solvent was removed and resulting sticky material redissolved in a methanol from which the product was crystallised using vapour diffusion with diethyl-ether.

2.11. trans-[Cu(II)H₄(N-en-S)₂] (BF₄)₂.OEt₂

Anal. Calc. for $C_{22}H_{32}N_2B_2CuF_8OS_2$: C, 41.17; H, 5.03; N, 4.36. Found: C, 41.45; H, 4.72; N, 4.97%. Mass spec. (ESI) m/z 393 [MH⁺]. $\lambda_{max} = 455$ nm, 601 nm.

2.12. trans-[Cu(II)H₄(N-pr-S)₂] (BF₄)₂

Anal. Calc. for $C_{20}H_{26}N_2B_2CuF_8S_2$: C, 40.52; H, 4.40; N, 4.76. Found: C, 40.10; H, 4.76; N, 4.42%. Mass spec. (ESI) *m/z* 421 [MH⁺]. λ_{max} = 436 nm, 595 nm.

3. Results and discussion

The *cis*-[Cu(H₄N₂S₂)]^{*n*+} Schiff base macrocycles were prepared using previously published methods [6,7,12]. They were hydrogenated using sodium borohydride to form the required amine macrocycles (Fig. 2). The macrocycles were obtained as sticky oily materials apart from *cis*-H₄N_{bu}S_{bu} which was obtained as an offwhite mass. All of the macrocycles gave suitable analysis by NMR and mass spectrometry and were subsequently used without further purification. They were converted into their respective copper complexes by treating them with copper(II) tetrafluoroborate. The majority of the complexes were obtained in their divalent form, apart from *cis*-[Cu(H₄N_{bu}S_{en})]⁺, which was obtained in its monovalent form (Fig. 3). Consistent with our previous studies on Schiff base macrocycles [6], the stability of the complexes is reduced as the ring sizes increase and consequently we were unable to synthesise *cis*-[Cu(H₄N_{pr}S_{bu})]²⁺ and *cis*-[Cu(H₄N_{bu}S_{bu})]²⁺.

The ¹H NMR of *cis*-H₄N_{bu}S_{bu} is extremely complex, indicative of a compact folded structure.⁵ As the ring size increases, folding of the organic chains for the neutral species becomes more favourable and the energy of metal internalisation falls. During protracted efforts to generate *cis*-[Cu(H₄N_{bu}S_{pr})]²⁺, we were able to retrieve small amounts of the protonated ligand (H₆N_{bu}S_{pr} (BF₄)₂) and an unexpected *exo*-complex of copper(II) chloride (Fig. 4). Consequently it appears that metal-centred complex formation is no longer favourable with these macrocycles. A similar observation regarding the limiting effects of large rings was reported for the parent Schiff base macrocycles [6].

In order to gauge the effect of the position of the donor atoms, two *trans*- $[Cu(H_4N_2S_2)]^{n+}$ amine complexes were also prepared (**13**, **14**). These were constructed using the template approach (Fig. 5) [7,12]. Equimolar amounts of **11** were mixed with **12** (Fig. 5), in an attempt to prepare the mixed en/pr complex, based on the premise that the statistical distribution would lead to a significant

proportion of the desired complex, which could then be separated from the mixture. However, mass spectroscopy suggested that the symmetric en/en and pr/pr complexes were dominant, and it was not possible to retrieve the mixed species in sufficient amounts and at an acceptable level of purity. Suitable crystals of *trans*-[Cu(II)H₄(N-pr-S)₂] (BF₄)₂ for X-ray analysis could also not be generated. However, comparison of the spectroscopic data (visible reflectance, mass spectrometry) with that of *trans*-[Cu(II)H₄(Nen-S)₂] (BF₄)₂, the reports of Bentfield et al. [10] and Martin et al. [12] and to a lesser extent the *cis* macrocycles (Fig. 3), indicate that it has an iso-structural motif.

3.1. Structure of the macrocyclic complexes

The smallest member of the series of complexes under investigation here, cis-[Cu(H₄N_{en}S_{en})]²⁺, has been reported previously [10]. X-ray quality crystals of the BF₄⁻ salts of cis-[Cu(H₄N_{pr}S_{en})]²⁺, $cis-[Cu(H_4N_{pr}S_{pr})(OH_2)]^{2+}$, $cis-[Cu(H_4N_{en}S_{pr})]^{2+}$ and $cis-[Cu(H_4N_{bu}-M_{bu})^{2+}]^{2+}$ S_{en})]⁺ were successfully isolated, thus expanding the catalogue of this family of compounds sufficiently for us to investigate the nature of the copper binding site (Fig. 3). For the divalent species, the copper typically sits in an almost planar environment, apart from $[Cu(H_4N_{en}S_{en})]^{2+}$, where the placement and nature of the donor atoms within the small 14-membered ring enforces a slight distortion at copper centre and small compression in the Cu-S and Cu-N distances (Table 2). The larger rings afford greater flexibility and this distortion is absent. During the early stages of this work we also synthesised $[Ni(H_4N_{pr}S_{en})Cl(OH_2)]^+$ using an approach reported by Lindoy and Smith [11]. In this instance H₄N_{pr}S_{en} ligand occupies the meridial plane of the nickel and it is notable that the metrical parameters in this region are indistinguishable from those observed for the three new copper macrocycles.

Of the three additional structurally characterised species, *cis*- $[Cu(H_4N_{pr}S_{en})]^{2+}$ and *cis*- $[Cu(H_4N_{en}S_{pr})]^{2+}$ contain orientated BF₄⁻

Fig. 2. A schematic representation of the synthesis of the cis- $[Cu(H_4N_2S_2)]^{n+}$ (n = 1, 2) Schiff base and amine macrocycles. Charges and oxidation states are omitted as individual species can exist in either of both forms.





Fig. 3. The X-ray crystal structures of cis- $[Cu^{II}(H_4N_{pr}S_{en})]^{2+}$, cis- $[Cu^{II}(H_4N_{pr}S_{pr})(OH_2)]^{2+}$, cis- $[Cu^{II}(H_4N_{en}S_{pr})]^{2+}$, cis- $[Cu^{II}(H_4N_{pr}S_{en})]^{2+}$

anions. These sit above and below the plane of the CuN₂S₂ motif at fixed positions with a fluoride in an axial position. The positions of the fluorines (\sim 2.5 Å) are typical of this type of interaction.¹ In particular they are not dissimilar to the Cu–Cl distance (Table 2) found in *cis*-[Cu(H₄N_{pr}S_{en})Cl]⁺, which is formed when HCl is used to isolate the ligand. The third species, *cis*-[Cu(N_{pr}S_{pr})(OH₂)]²⁺ (Fig. 3), is different in that it is five coordinate with a water molecule occupying the

axial position. Occupation of this site means that, in this instance, there is only space for one weakly bound BF_4^- counter ion.

The copper species became more difficult to generate as the ring size increased. Significantly, cis- $[Cu(H_4N_{bu}S_{en})]^+$ was isolated in its univalent form (Fig. 3) and as expected the macrocyclic ligand reorganises to accommodate the tetrahedral preference of the d¹⁰ ion. The movement of the ligand to accommodate the univalent cation forces the ligand to move from the plane occupying donor sites that sit on the circumference of a circle (~4.8 Å diameter; data for cis- $[Cu(H_4N_{pr}S_{pr})]^+$) to the points of a tetrahedron which can be considered to occupy points on the surface of a sphere (~4.6 Å

 $^{^1}$ 45 of the 66 structures deposited in the crystallographic database (Feb. 2009) which contain copper and tetrafluoroborate have Cu–F distances within the limits of the range (2.4–2.8 Å) defined by the complexes reported here.



Fig. 4. The X-ray crystal structures of $[CuCl_2(cis-H_4N_{bu}S_{pr})_2]^{2+}$ and $[H_6N_{pr}S_{bu}]^{2+}$. $[CuCl_2(cis-H_4N_{bu}S_{pr})_2]^{2+}$ is an *exo*-complex where incorporation of the metal within the ring or between pairs of donors is no longer favoured. The source of the halides is unknown.



Fig. 5. A schematic representation of the synthesis of the *trans*-N₂S₂ Schiff base macrocycle. These were hydrogenated as described above to form the relevant amine macrocycle.

diameter). The necessary twist in the ligand required to reach these positions requires that the diameter of the pocket in which the metal sits changes. Thus, rather than the expected expansion in the Cu-S and Cu-N distances with the larger, reduced metal centre, we find that there is a small contraction in the Cu-S and Cu-N bond distances as compared to the divalent complex cis- $[Cu(H_4N_{pr}S_{pr})]^+$, which has the same number of atoms in the ring. A similar effect has been commented on by Nanda et al. [17] and was reported in our studies on Schiff base macrocycles [6]. Another notable similarity to the behaviour of this family of complexes with their parent Schiff base complexes is the influence of the polymethylene spacers between the nitrogen donors. Expansion here forces the macrocycle out of the plane, favouring a tetrahedral form and thus copper(I). This effect is not seen with the corresponding complex $[Cu(H_4N_{en}S_{bu})]^{2+}$, which has the butylene group between the sulphur donors. Unfortunately, increasing the ring's size to 17, i.e. $[Cu(H_4N_{bu}S_{pr})]^{2+}$ compromises the stability of the macrocyclic complex and it was not possible to produce a viable complex from the standard reaction scheme (Fig. 2). By resorting to alternative counter ions, a small amount of complex was obtained and characterised (Fig. 4). Here, the bonds to sulphur do not form and the metal centre remains in an exo-position. Two chlorides are found in the coordination sphere despite the absence of chloride salts in the reaction mixture. The halide probably arises from the chlorinated solvents. Since the desired complex did not form, the problems encountered in the synthesis of $[CuCl_2(cis-H_4N_{bu}S_{pr})_2]^{2+}$ are of little relevance at this stage, and we have not investigated this finding further.

The two *trans*- $[Cu(N_2S_2)]^{2+}$ amines were also isolated. *trans*- $[Cu(H_4N-en-S)_2]^{2+}$ has been reported previously as the perchlorate salt [12]. We have been trying to avoid the presence of oxidising ligands such as perchlorate in our work as they might interfere in the ensuing chemical reactions and we have hence prepared the $[BF_4]^-$ salts. In our previous experience, changing the counter anions has little effect on the structures of these entities, and the mass spectrometry and visible spectroscopy of both complexes, *trans*- $[Cu(H_4N-en-S)_2]^{2+}$ and *trans*- $[Cu(H_4N-pr-S)_2]^{2+}$ indicate that the desired complexes have been formed.

4. Electrochemical studies

The amine macrocycles reported here remain relatively flexible (compared to simple macrocycles reported previously in 2 & 3) and appear to be able to adjust to the geometric preferences of the encapsulated metal (Cu(I), tetrahedral; Cu(II), planar). We were thus interested to investigate the electrochemical behaviour of these geometrically accommodating macrocyclic complexes in

vere encountered with the [BF	[4] ⁻ anions asso	ciated with cis-[Cu(H4N _{bu} S _{en})] ⁺ , ¿	as stated in Ta	ble 1. Esd's arc	e only for the c	compounds reported here.	D denotes the relevant axial	donor e.g. (BF_4^{-}) , O	(OH ₂), Cl.	
Complex	M-N (Å)	M–S (Å)	N–M–S (°) trans	(°)	N-M-S (°) cis	S-M-S (°)	Notional torsion angles N-N-S-S (°)	Displacement Cu from N–N–S–S plane (Å)	D_{ax} –M– D_{ax} (°)	M…F (Å)	M-D _{axial} (Å)
cis-[Cu(H ₄ N _{en} S _{en})] ⁺ [10]	2.015 2.014	2.277 2.234	133.4 139.2	89.66	102.72 100.98	98.10	55.02	n/a			
cis-[Cu(H ₄ N _{en} S _{en})] ²⁺ [10]	1.987 1 989	2.293 2.293	156.4 160.2	86.78	95.01 95.36	90.86	30.28	0.035			
cis-[Cu(H ₄ N _{pr} S _{en})] ²⁺	2.036(4)	2.326(1)	169.2(1)	94.5(2)	91.6(1)	83.67(4)	10.6(1)	0.318(16)	175.96	2.406	
cis-[Cu(H ₄ N _{bu} S _{en})] ⁺	2.046(4) 2.022(4)	2.399(1) 2.292(1)	172.3(1) 117.1(1)	117.2(1)	91.2(1) 100.6(1)	95.41(5)	-61.83(8)	n/a		2.743	
cis-[Cu(H ₄ N _{prSpr})(OH ₂)] ²⁺	2.029(4) 2.027(3)	2.298(1) 2.3288(8)	124.6(1) 173.83(9)	88.8(1)	100.8(1) 90.85(8)	89.54(3)	7.86(9)	0.012(1)	n/a		2.395(3)
cis-[Cu(H ₄ N _{en} S _{nr})] ²⁺	2.037(3) 2.005(4)	2.3607(9) 2.230(2)	175.07(9) 174.3(1)	86.3(2)	91.34(8) 93.0(1)	88.07(5)	0.6(2)	0.097(2)	173.21	2.433	
-ind s N H).	2.016(4)	2.368(1) 2.364(3)	175.1(1) 166 5(2)		93.2(1)					2.483	2 ADD(A)
cio-locititititution	2.058(7)	2.397(4)	171.4(2)								(+)00+-7
cis-[Ni(H ₄ N _{prSen})Cl(OH ₂)] ⁺	2.065(2)	2.4320(8)	172.17(7)						178.28(7)		2.134(2) -0
	2.081(2)	2.4468(8)	172.71(7)								2.3907(7) –Cl

comparison to their more rigid parent Schiff base macrocycles, which are more limiting for the metal centre geometry [6]. Consequently, this aspect of the study was carried out in organic solvent to allow comparison of the data for the two types of macrocycles. However, the enhanced water stability and solubility of these *cis*-amine thioether complexes also allowed us to study their behaviour in aqueous solution. This was important to the underlying aim to obtain copper complexes with potential for use in biological systems.

In non-aqueous solvent the oxidation potentials of the amine macrocycles are observed to display a comparable range $(\sim 0.32 \text{ V})$ to that of their analogous Schiff base species $(\sim 0.38 \text{ V})$. However, although the replacement of the imine (-0.42 to (0.04 V) with a secondary amine (-0.68 to -0.36) does produce the expected anodic shift in $E^{1/2}$ [4,18] (Cu^I/Cu^{II}) the corresponding values suggest that the change is not uniform. Indeed the two complexes based on the $N_{en}S_{en}$ are observed to have a comparable $E^{1/2}$. Similarly, the two series of complexes based on Sen have widely differing behaviour. While the Schiff base complexes show a marginal rise in $E^{1/2}$ as the macrocyclic ring size increases, the amine macrocycles do not follow a definite pattern. Repeating the experiment in aqueous solution we observed a solvent-dependent shift in all the $E^{1/2}$ values recorded (Table 3). This probably arises from the polarity differences between the two solvents. This is particularly apparent in the values for $[Cu(H_4N_{pr}S_{en})]^{2+}$, with an $E^{1/2}$ value in acetonitrile of -0.15 V (the lowest w.r.t Ag wire), whereas in aqueous solution this species gave the highest value (0.16 w.r.t Ag wire). The reason for this non-uniform change is unclear but probably stems from the manner in which the copper macrocycle solvates (Fig. 3). Based on this observation it is surprising that this species was not isolated in the copper(I) form (cf. cis- $[Cu(H_4N_{bu}S_{en})]^+).$

It was not possible to investigate the geometric effects (bond length, bond angles, torsion angles) underlying the shift in $E^{1/2}$ in the Schiff base macrocycles synthesized previously, as this family of species were isolated in both mono and divalent forms [6]. However, a subset of the compounds reported here, cis-[Cu(H₄N_{pr}- S_{en})]²⁺, *cis*-[Cu(H₄N_{pr}S_{pr})(OH₂)]²⁺, *cis*-[Cu(H₄N_{en}S_{pr})]²⁺, and the previously reported cis-[Cu(H₄N_{en}S_{en})]²⁺ [10] were all isolated in their divalent form (Fig. 3, Table 2). Focusing on these divalent species we find that the bond lengths (Cu-N, Cu-S) generally increase with ring size and that the notional torsion (measured through N-N–S–S) and simple bond angles (D–Cu–D at \sim 90° D = donor atom) all move to a less strained conformation (i.e. 0° and 90°, respectively) as the ring size increases (Supplementary material). These observations are in line with previous studies on S₄ and N₄ macrocyclic complexes of copper and cobalt [19-21]. Studies on these highly flexible (S₄ and N₄) ligand complexes have further investigated the effects of torsion angles, bond angles and bond distance on $E^{1/2}$ of these species [19–21]. These homoatomic donor species are chemical extremes of the heteroatomic N₂S₂ donor set being reported here. Consistent with these studies, we also observe a small increase in $E^{1/2}$ as the torsional strain increases (Fig. 6). The effect of bond angle and bond length is more interesting. In acetonitrile, we observe an increase in $E^{1/2}$ as the Cu–N and Cu–S distances increases. However, this effect is absent in water, suggesting that the solution phase species in the two solvents differ (e.g. $[Cu(H_4N_2S_2)]^{2+}$ vs $[Cu(H_4N_2S_2)(OH_2)]^{2+}$, Fig. 3). A pronounced effect of the >S–Cu–S angle on $E^{1/2}$ is also observed, suggesting that we can raise the $E^{1/2}$ by making the angle more obtuse. While this is true in both acetonitrile and water, the corresponding influence of <N-Cu-N on $E^{1/2}$ is markedly different in the two solvents. In acetonitrile $E^{1/2}$ falls as the angle increases, whereas in water it falls as the angle becomes more acute. This supports the argument that the solution phase species in these solvents differ. However, it also emphasises the care that should be taken in correlating the

Table 3 Electrochemical data for the *cis/trans* $Cu[(H_4N_{xx}S_{yy})]_n^{n+}BF_4$ complexes.

	MeCN (V) ^a	Water (V) ^b	Corresponding Schiff base in $MeCN^{c}(V)$	Potential vs.	Potential vs. Ag wire ^d		
				Ring size	MeCN (V)	Water (V)	
Cu(II) cis-H ₄ N _{en} S _{en} ·2BF ₄	-0.36	-0.10	-0.42	14	0.17	-0.01	
Cu(II) cis-H ₄ N _{pr} S _{en} ·2BF ₄	-0.68	0.04	-0.04	15	-0.15	0.16	
Cu(II) cis-H ₄ N _{pr} S _{pr} .(OH ₂)·2BF ₄	-0.48	-0.14	-0.34	15	0.05	0.02	
Cu(II) cis-H ₄ N _{en} S _{pr} ·2BF ₄	-0.48	-0.19	-0.40	16	0.05	-0.03	
Cu(II) cis-H ₄ N _{en} S _{bu} ·2BF ₄	-0.40	-0.03		16	0.13	0.04	
Cu(II) trans-H ₄ N _{en} S _{en} ·2BF ₄	-0.52	Insol.	-0.26	14			
Cu(II) trans-H ₄ N _{pr} S _{pr} ·2BF ₄	-0.36	Insol.	-0.03 (Cu(I))	16			

^a Acetonitrile (0.1 M ^tBu₄NBF₄: potentials reported vs. ferrocene at 100 mV/s).

^b Water (0.1 M NaCl: potentials reported vs. $[Fe(CN)_6]^{3-}$ at 100 mV/s). The *trans*-amine macrocycles were not sufficiently soluble (insol.) in water for analysis.

^c Data collected for the related Schiff base complexes in acetonitrile (0.1 M 'Bu₄NBF₄: potentials reported vs. ferrocene at 100 mV/s).

^d For comparison between solvents, potentials are also reported vs. Ag wire.



Fig. 6. The notional torsion angles (N–N–S–S), bond angles (at 90°) and the metal donor bond distances for *cis*–[Cu(H₄N_{pr}S_{en})]²⁺, *cis*–[Cu(H₄N_{pr}S_{pr})(OH₂)]²⁺, *cis*–[Cu(H₄-N_{en}S_{pr})]²⁺ and *cis*–[Cu(H₄N_{en}S_{en})]²⁺ [10] plotted as a function of $E^{1/2}$. Simple regression lines are drawn only for data sets which show some proportional change between $E^{1/2}$ and the metric being plotted.

metrical parameters derived from the crystallographic data and the $E^{1/2}$. Indeed, the results presented here suggest that in water these complexes will be five coordinate with a water molecule filling the

fifth coordination site. However, the formation of acetonitrile adducts cannot be ruled out. Indeed an acetonitrile adduct of the copper(II) Schiff base macrocycle derived from $N_{pr}S_{en}$ has been reported [6].

The values obtained for the two *trans*-amine complexes lie at the extremes of the ranges reported (Table 3). It has been reported previously [18] that the *trans* disposition of the donors in N_2S_2 complexes creates a more confined metal binding pocket compared to the respective *cis* analogues. This could contribute to the difference observed.

5. Concluding remarks

The family of $[Cu(H_4N_2S_2)]^{n+}$ macrocycles have been structurally characterised. Electrochemical analysis suggests that in these amine complexes the redox potential is not heavily influenced by ring size. This contrasts with our previous study employing Schiff base macrocycles, where an effect of ring size on redox potential was detected [6]. Furthermore, the anomalous behaviour of [Cu(H₄N_{pr}S_{en}]⁺ indicates that more subtle effects may be involved, which we might expect to translated into their chemical behaviour. Our ability to obtain redox potentials from aqueous solution suggests that, unlike their Schiff base analogues, these complexes should have some utility as redox sensors for biological applications. While it is evident that ring sizes in excess of 17 can be expected to be unstable, the disparate electrochemical behaviour of the remaining rings suggests that it is unwise to focus efforts on a single ring size. Unlike their Schiff base and tetrathioether [19,20] analogues, the aqueous solubility and stability of these amine-thioether species suggest that they should be stable enough to withstand reactions with biologically-relevant reducing (e.g. ascorbate, glutathione) and oxidising agents (hypochlorite and hydrogen peroxide), and the future aim of our work is to test this hypothesis.

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Appendix A. Supplementary material

CCDC 738881-738888 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2010.01.012.

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Glossary

- cis-H₄N_{en}S_{en}: 5,6,13,14-bisbenzo-8,11-diaza-1,4-dithia-cyclotetradecane
- cis-H₄N_{pr}S_{en}: 5,6,14,15-bisbenzo-8,12-diaza-1,4-dithia-cyclopentadecane
- *cis*-*H*₄*N*_{bu}S_{en}: 5,6,15,16-bisbenzo-8,13-diaza-1,4-dithia-cyclohexadecane
- cis-H₄N_{en}S_{pr}: 6,7,14,15-bisbenzo-9,12-diaza-1,5-dithia-cyclopentadecane
- cis-H₄N_{pr}S_{pr}: 6,7,15,16-bisbenzo-9,13-diaza-1,5-dithia-cyclohexadecane
- cis-H₄N_{bu}S_{pr}: 6,7,16,17-bisbenzo-9,14-diaza-1,5-dithia-cycloheptadecane cis-H₄N_{en}S_{bu}: 7,8,15,16-bisbenzo-10,13-diaza-1,6-dithia-cyclohexadecane
- cis-H₄N_{pr}S_{bu}: 7,8,16,17-bisbenzo-10,14-diaza-1,6-dithia-cycloheptadecane cis-H₄N_{bu}S_{bu}: 7,8,17,18-bisbenzo-10,15-diaza-1,6-dithia-cyclooctadecane
- trans-H₄(N-en-S)₂: 6,7,13,14-bisbenzo-4,11-diaza-1,8-dithiacyclotetradecane trans-H₄(N-pr-S)₂: 7,8,15,16-bisbenzo-5,13-diaza-1,9-dithiacyclohexadecane