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Synthesis and characterization of 1,8-dithia-4,11-diazacyclotetradecane

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ABSTRACT

The synthesis of 1,8-dithia-4,11-diazacyclotetradecane **L_3**, a member of a series of [14]aneN_2S_2 ligands, has been synthesized and characterized. The crystal structures of [1,8-dithia-4,11-diazacylotetradecane] **L_3** and [1,8-dithia-4,11-diazayclotetradecane dihydrochloride] **L_3·2HCl** are presented.

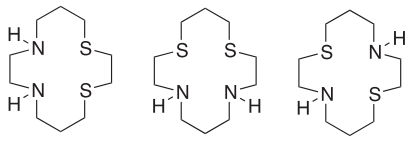
Following the structural characterization and analysis of Blue Copper Proteins[1], macrocyclic ligands have attracted much interest as simple models for naturally occurring metal-macrocycle centers.[2] Several macrocyclic systems such as polythiaethers,[3] polyazacycloalkanes,[4] thia-aza,[5] and trithiaethers[6] have been synthesized and investigated as synthetic analogs to date.[7] These ligands are also attractive for their enhanced stability with metal ions when compared to the acyclic versions. The enhanced stability, termed the 'macrocyclic effect' is in large part due to the donor ligands being fixed in their orientation when compared to the acyclic counterparts, which have higher degrees of freedom.[8–10]

These ligands have not only been investigated as analogs for metal protein interactions, but they have also been examined in medicinal chemistry as anti-parasitic drugs, in biomedical applications, such as MRI contrast-enhancing agents and as therapeutic agents in chelate therapy for metal intoxication, and ionophores.[11]

As reported by Siegfried and Kaden, the ideal N_2S_2 ligand has a ring size of 14 with an alternating 2,3,2,3 arrangement of connecting atoms for the complexation of Cu^{2+} which allows for minimal structural distortion.[12]

The three possible N–S mixed donor ligands 1,4-dithia-8,11-diazacyclotetradecane **L_1**, 1,11-dithia-4,8-diazacyclotetradecane **L_2**, and 1,8-dithia-4,11-diazacyclotetradecane **L_3**, are shown in Figure 1. All three ligands have been mentioned throughout literature; however, only the synthesis of **L_1** has been reported to date.[12] The synthesis of a di-benzo 14-membered macrocycle related to **L_3** was reported by Wild, which employed the reduction of a di-benzo *trans* Schiff base precursor.[13] However, the synthesis and characterization of the parent ligand 1,8-dithia-4,11-diazacyclotetradecane have not been reported to date. This is likely due to the alternating arrangement of the thia-aza donor atoms rendering the simple capping/condensation methods that are currently in place for making thia, aza, and oxa crowns inappropriate due to potential isomer formation.[14]

Reported here is the synthesis of 1,8-dithia-4,11-diazacyclotetradecane **L_3** via a convergent approach depicted in Scheme 1. The primary amino groups of the starting material, cystamine dihydrochloride **1** were protected with *p*-toluenesulfonyl chloride in 90% yield.[15] The tosylamide was chosen not only for its stability but to also aid in the cyclization through its electronic effect. The



L_1 L_2 L_3

Figure 1. 14-membered mixed N-S donor types.

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† Information regarding crystallography on compound **L_3**.

‡ Mass spectrometry.

§ Information regarding crystallography on compound **L_3·2HCl**.

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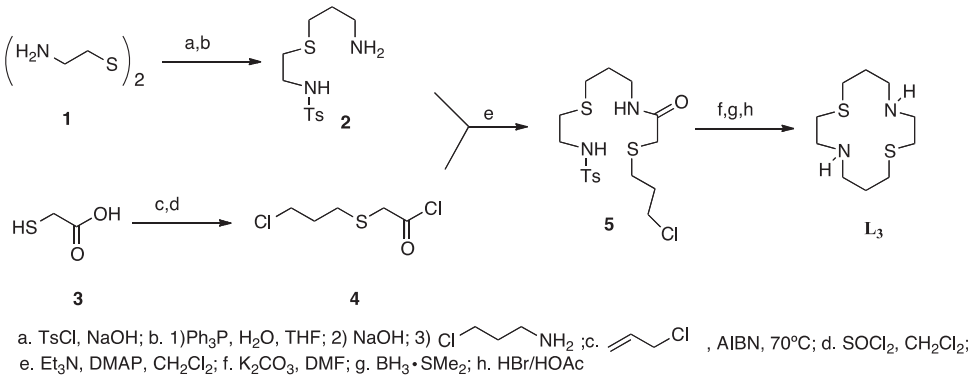

Scheme 1. Synthesis of 1,8-dithia-4,11-diazacyclotetradecane.

tosyl group makes it possible to deprotonate the tosylamide thus creating a good nucleophile for the macrocyclization. Cleavage of the disulfide bond using triphenylphosphine resulted in the formation of the intermediate thiol in situ.[16,17] The thiol was converted into the thiolate with aqueous NaOH and alkylated with 3-chloro-1-aminopropane to afford **2** in 95% yield.

The second intermediate 2-[(3-chloropropyl)sulfanyl]acetyl chloride **4** was synthesized by radical addition of mercaptoacetic acid **3** to allyl chloride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) to give the acid which was directly converted into the acid chloride using thionyl chloride. Purification by vacuum distillation produced **4** in 87%.[18]

Amine **2** undergoes acylation in CH_2Cl_2 with triethylamine, a catalytic amount of 4-dimethylaminopyridine (DMAP), and acid chloride **4** to produce the uncyclized amide **5** as a yellow oil, isolated in 91% yield after chromatography.[19] The intramolecular cyclization was performed by adopting a modified Kellogg's procedure,[20] to achieve relatively dilute conditions with slow addition times. Either K_2CO_3 or Cs_2CO_3 can be employed as the base in DMF at 100 °C. The resulting amide macrocycle is purified by recrystallization in 58% yield.

Reduction of the tosylamide was accomplished using 2 equiv of borane dimethyl sulfide in refluxing toluene.[21] Following the reduction, triethanolamine in methanol was added and the reaction then refluxed for an additional 48 h to decompose the amine-borane complex. Purification by column chromatography yielded 85% of the tosylamine. Detosylation was carried out using 33% HBr in acetic acid in the presence of phenol to give the desired free amine **L_3** after basic workup.[22] The amine was recrystallized from ethyl acetate in 87% yield producing a tan solid.

Crystals of **L_3** suitable for X-ray diffraction were grown from ethyl acetate. The crystal structure of **L_3** is shown in Figure 2. Compound **L_3** crystallizes in the triclinic space group P-1 and adopts a [3434] conformation according to Dale's notation.[23] The ring adopts a rectangular endodentate conformation with carbon atoms at the corners instead of the heteroatoms. The nitrogen atoms in the ring are located in the center of the 4-atom connecting chains with their hydrogens pointing toward the ring cavity. The crystal structure of cyclam, reported by Raston, shows similar hydrogen orientations for the nitrogens at the 4,11 positions with the exception that it also contains intramolecular hydrogen bonding interactions.[24] The N–N bond distance between the 4,11 positions through the cavity is ~4.69 Å and the S–S is ~5.25 Å. The S–N at the 1,4 positions is ~3.13 Å and the S–N at the 4,8 positions is ~3.86 Å.

To further examine the structural characteristics of the ring, the amine hydrochloride salt **L_3·2HCl** was synthesized. The amine hydrochloride salt precipitated out as fine white crystals from a 50/50 mixture of ethanol/water. The crystal structure of **L_3·2HCl** is also shown in Figure 2. The crystal system is monoclinic with a space group of P2(1)/n and contains one molecule in the asymmetric unit. The di-protonated form of the macrocycle adopts an exodentate conformation with the heteroatoms located at the

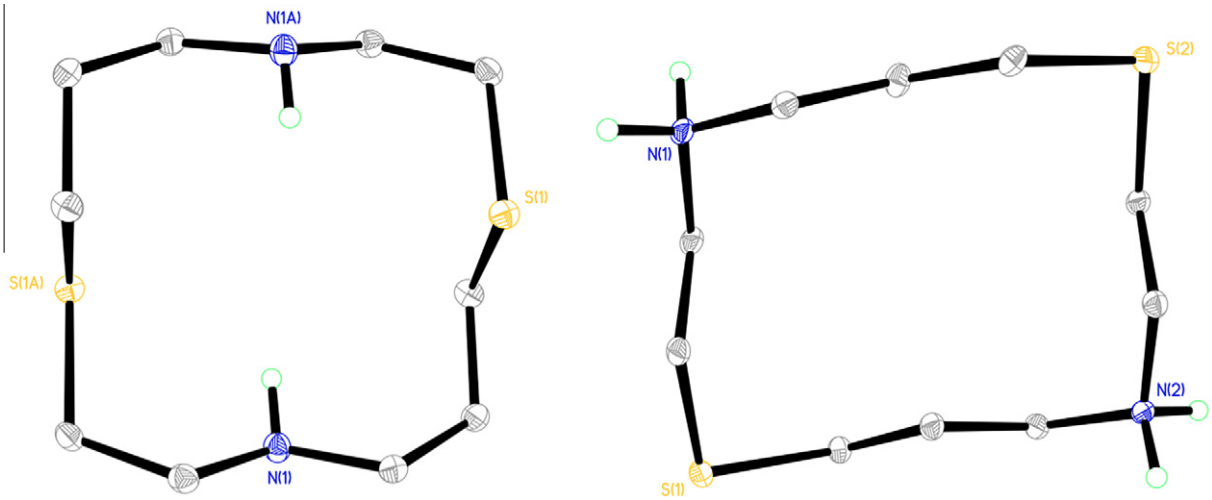

Figure 2. The structures of 6 from EtOAc and 6·2HCl from ethanol:water with 35% thermal ellipsoids. Hydrogen atoms with the exception of N–H positions have been omitted for clarity.

Table 1
Crystal data and structure refinement for **L_3** and **L3·2HCl**

Identification code	L_3	L_3·2HCl
Empirical formula	C_{10} H_{22} N_2 S_2	C_{10} H_{26} Cl_2 N_2 O S_2
Formula weight	234.42	325.35
Crystal System	Triclinic	Monoclinic
Space group	P-1	P2(1)/n
Unit cell dimensions	5.3666(9) Å	7.6164(6) Å
	7.8306(13) Å	13.3949(11) Å
	8.5240(14) Å	15.6467(13) Å
	115.552(2) °	90°
	106.336(3) °	102.710(3)°
	93.256(3) °	90°
Volume	303.49(9) Å^3	1557.2(2) Å^3
Z	1	4
Density (calculated)	1.283 Mg m^{-3}	1.388 Mg m^{-3}
Absorption coefficient	0.406 mm^{-1}	0.674 mm^{-1}
F(000)	128	696
Crystal size	0.34 × 0.18 × 0.09 mm^3	0.47 × 0.15 × 0.14 mm^3
Index ranges	$-7 \leqslant h \leqslant 7$	$-9 \leqslant h \leqslant 7$
	$-10 \leqslant k \leqslant 10$	$-15 \leqslant k \leqslant 11$
	$-11 \leqslant l \leqslant 11$	$-18 \leqslant l \leqslant 18$
Reflections collected	2721	10183
	1412	2756
Independent reflections	[R(int) = 0.0270]	[R(int) = 0.0352]
Data/restraints/ parameters	1412/0/68	2756/0/162
Goodness-of-fit on F^2	1.064	0.705
Final R indices [$I > \sigma(I)$]	R_1 = 0.0381	R_1 = 0.0311
	wR_2 = 0.0943	wR_2 = 0.0765
R indices (all data)	R_1 = 0.0401	R_1 = 0.0498
	wR_2 = 0.0964	wR_2 = 0.0921
Largest diff. peak and hole	0.412 and −0.347 e Å^{-3}	0.284 and −0.232 e Å^{-3}

Table 2
Key bond distances and angles for **L_3** and **L_3·2HCl**

Bond lengths, Å	L_3	L_3·2HCl
S–C	1.8117(16), 1.8154(16)	1.807(2), 1.820(3), 1.807(2), 1.817(2)
N–C	1.459(2), 1.461(2)	1.501(3), 1.497(3), 1.491(3), 1.501(3)
C–C	1.522(2), 1.528(2), 1.523(2)	1.521(3), 1.519(3), 1.524(3), 1.520(3)1.512(3), 1.524(3),
Bond angles°		
C–S–C	100.71(7)	102.47(12), 102.09(12)
C–N–C	112.48(12)	117.23(19), 116.30(19)
C–C–S	114.74(11), 110.37(11)	113.32(17), 114.43(17), 112.27(16), 114.91(17)
C–C–C	114.68(13)	110.0(2), 109.4(2)
N–C–C	111.76(13), 110.94(13)	111.28(19), 112.8(2), 110.94(19), 112.23(19),

corners. Similar crystallographic data of the tetra-protonated form $[H_4(cyclam)]^{4+}$ were also reported by Raston.[24] A comparison of **L_3** and **L_3·2HCl** crystal data and structure refinement parameters are given in Table 1 and key bond distances and angles are reported in Table 2.

In conclusion we have successfully synthesized ligand **L_3** in good overall yield. Ligand **L_3** is currently undergoing copper and chelation studies, and is also being employed as the framework for the syntheses of several cryptands. These studies will be reported in due time.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.088.

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