

Appendix 5

Syntheses, Crystal Structures and Coordination Abilities of New Macrocyclic Ligands N-Substituted with Functional Groups

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ABSTRACT

Three new macrocyclic ligands N-substituted with various types and numbers of pendant arms: 1,12-diaza-3,4: 9,10-dibenzo-5,8-dioxyacyclopentadecane-N-acetic acid (L_2); 1,12-diaza-3,4: 9,10-dibenzo-5,8-dioxya-cyclopentadecane-N-cyanoethyl(L_4) and 1,12,15-triaza-3,4: 8,9-dibenzo-5,8-dioxa-cyclooctadecane-N-ethanoamine(L_6) have been synthesized and characterized by single crystal X-ray diffraction analysis. The results of X-ray diffraction analysis show that the crystal structure of L_2 is triclinic system, space group $P\bar{1}$ with $a=8.6083(1)$, $b=11.9827(3)$, $c=12.8734(3)$ Å, $V=1222.54(6)$ Å³, $Z = 2$. Refinement of the atomic parameters by least-squares techniques gives a final R factor: $R=0.0961$. The crystal structure of L_6 is monoclinic system, space group $P2(1)/n$ with $a=11.5815(2)$, $b=10.6063(2)$, $c=19.4601(1)$ Å, $V=2317.97(6)$ Å³, $Z = 4$, $\lambda(\text{MoK}\alpha) = 0.71073$, $R=0.0338$. Coordination ability of these new macrocyclic ligands N-substituted with various functional groups to transition metal Co, Ni, Cu, Zn and Cd are also discussed. The results show that the coordination ability of L_2 and L_6 are stronger than that of parent macrocyclic ligands, but coordination abilities of L_4 are weaker than that of parent macrocyclic ligand, L_2 and L_6 .

Introduction

Selective complexing of macrocycle ligands with mixed nitrogen and oxygen to some specific metal ions is one of the important and rapidly expanding projects of research[1] because of their important applications in many scientific areas. For example, 1,4,7,10-tetraazamacyclodecane macrocyclic lanthanide complexes were applied as MRI contrast agents[2], NMR shift reagents[3] and RNA cleavage catalysts [4]. Therefore it is very significant sense to find new functional macrocycle ligands with interesting chemical, biological or catalytic properties.

Recently some macrocyclic ligands with various pendant arms such as acetate acid [5], methanephosphonic acid[6] and ferrocenylmethyl[7] have been synthesized, and the stability of their complexes has been studied. The reports[8] on complexes of 12- to 14-membered rings have shown that the increase in the size of cavity of macrocycle with N-substituting groups cause a sharp decrease in the stability of complexes for some metal ions, such as Mn^{2+} and Pb^{2+} . However, for the other ions, such as Fe^{2+} and Zn^{2+} , the stability of those complexes is not affected. Lindoy and other workers have discussed the effect of macrocycle with mixed nitrogen and oxygen and macrocycle-based ligands with various carboxyl acid arms on thermodynamic stability and selectivity [5]. In an attempt to study new macrocyclic derivatives N-substituted with various pendant arms, we synthesized and characterized three new 15- or 17-membered macrocyclic ligands with a specific group of ethylamine, acetate acid or cyanoethyl in this paper. The protonation constants of these ligands and their stability constants of complexes with some transition metal ions were determined. The results demonstrate that 15- or 17-membered functional ligands are more selective for the first-row transition-metal ion compared with the corresponding 12- to 14-membered rings. The structures of newly-synthesized three ligands and analogous ligands are shown in Fig.1.

Experimental

All chemical reagents were commercial products of analytical grade. All solvents were purified by conventional methods. 1,2-bis(2-formylphenoxy)ethane(compound 1) was synthesized according to the method reported previously[9].

Microanalyses were carried out on a Perkin-Elmer 240C an Elemental Analyzer. IR spectra were recorded on a Fourier Transfer Infrared Spectrometer (Bruker, Vector 22) as KBr pellets. Fast atom bombardment mass spectra were recorded on a VG auto-Spec instrument using Cs as fast atoms.

Syntheses of L₂

Ligand L₂ was synthesized according to the method reported previously[10], Yield, 54%, m.p. 135.5 °C (Found: C, 60.7; N, 7.5; H, 6.7. C₂₁H₃₁N₂O_{6.5} Calc.: C, 60.6; N, 7.5; H, 6.8. IR (KBr, cm⁻¹): 3230 (N-H), 1632(C=O), ¹H NMR(D₂O): 1.73(2H, CH₂COO), 1.91(H, NH), 2.26-3.22(4H, NCH₂), 4.13(4H, ArCH₂), 4.38(4H, OCH₂), 7.35-6.68(8H, Ar). FAB MS: m/z 372.

Synthesis of L₄

2.70g (0.01mol) of ligand L₁ was added to acrylonitrile (80ml) and refluxed for 6 hours, then excess acrylonitrile was evaporated. Methanol-ether 50ml (2:3,v/v) was added and a white solid separated. The product was recrystallized with a mixture of acetic ether and ether (2:1,v/v), Yield 3.5g (85%), m.p. 109.5 °C (Found: C, 69.29; N, 12.51; H, 7.60. C₂₆H₃₄N₄O₃ requires C, 69.33; N, 12.44; H, 7.56. IR (KBr, cm⁻¹): 3280, (N-H), 2248(C≡N), ¹H NMR(CDCl₃): 1.63(4H, CH₂CN), 2.32-2.97(8H, NCH₂), 3.71(4H, ArCH₂), 4.38(4H, OCH₂), 7.35-6.68(8H, Ar). FAB-MS: m/z 418.

Synthesis of L₆

Tri(2-ethylamine)amine(tren) (0.72g, 5 mmol) in dry methanol(50ml) was added dropwise to a boiling solution of compound(1) (1.35g, 5 mmol) in dry methanol(150ml). The mixture solution was refluxed for 30 min, then allowed to cool. Excess sodium borohydride(2.5g)(plus a small amount of borax) was added slowly to the mixture solution, then the volume was reduced to 40ml. Water(100ml) was added and the oil product was separated. The solution of oil product in acetone was acidified to pH 6.5-7.5 with concentrated hydrobromic acid slowly. A white product precipitated and was washed with ether, Yield, 1.60g(78%), m.p. 188.5 °C. Found: C, 54.5; N, 11.7; H, 7.3. C₂₂H₃₅N₄O₃Br Calc.: C, 54.6; N, 11.6; H, 7.2. IR (KBr, cm⁻¹): 3328, 3233 (-NH₂), ¹H NMR(D₂O): 1.70(2H, CH₂NH₂), 1.96(2H, NH), 2.26-3.22(6H, NCH₂), 4.13(4H, ArCH₂), 4.38(4H, OCH₂), 7.35-6.68(8H, Ar), 8.23(2H, NH₂). FAB MS m/z 384.

Potentiometric Determination

Potentiometric measurements were carried out according to the procedure described elsewhere[11]. The potentiometric apparatus consists of a water-jacketed measuring cell with a glass electrode and a water-jacketed calomel reference electrode connected by using a salt bridge. The ionic strength of common supporting electrolyte is 0.10 mol·dm⁻³ adjusted with KNO₃(0.50 mol/L). The temperature for the measurement was maintained at 25±0.1 °C by a refrigerated circulating water bath. During each run, the solution was saturated with nitrogen. The solution in the measuring cell was stirred magnetically. Typical concentrations of experimental solutions were 2.00 × 10⁻³ mol·dm⁻³ for ligands and 0.100 mol·dm⁻³ for KOH, and the initial solution volumes were 50.0 cm³. Fifty to sixty experimental data points were recorded by titration for the measurement of protonation constants. Three groups of parallel titration were performed

for the determination of the standard deviation. Standard stock solutions were prepared from analytical grade metal salt, which were standardized by titration with ethylenediaminetetraacetate. The meter-glass electrode system was calibrated by standard acid with KCl at $0.100\text{mol}\cdot\text{dm}^{-3}$ as the supporting electrolyte to read hydrogen-ion concentration directly so that the measured value was $-\log[\text{H}]$.

Protonation constants of ligands and stability constants of complexes were determined by potentiometric titration under nitrogen, and calculated using program BEST[11]. Estimated errors for the stability constants are ± 0.02 , which were used to measure the deviation of experimental $\text{p}[\text{H}]$ data from the predicted values by equilibrium constants.

Crystallographic Data Collection and Structure Solution

The three dimensional data of the ligands were collected on a SMART CCD diffractometer using graphite monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) using ω -scans with a detector distance of 4cm and swing angle of -35° . A hemisphere of the reciprocal space was covered by combination of three sets of exposures; each set had a different ϕ angle ($0, 88, 180^\circ$) and each exposure of 30s covered 0.3° in ω . The collected data were reduced by using the program SAINT [12] and empirical absorption correction was carried out by using the SADABS [13] program. The data were collected up to the 2θ -values of 55° and 50° respectively.

The trial structures were obtained by direct methods using the program SHELXTL¹⁴ and refined by least-squares procedures on F^2 . All non-H atoms were refined anisotropically and the hydrogen atoms were fixed geometrically and allowed to ride on the parent carbon atoms. A total of 407 and 297 parameters were refined using 5290 and 4186 observed reflections [$I > 2 \sigma(I)$] for L_2 and L_6 , respectively. Sigma weighting

schemes, [$w = 1/[\sigma^2(\text{Fo}^2) + (0.05777\text{P})^2 + 0.9358\text{P}]$], where $\text{P} = (\text{Fo}^2 + 2\text{Fc}^2)/3$ and $w=1/[\sigma^2(\text{Fo}^2) + (0.1621\text{P})^2 + 1.3230\text{P}]$, where $\text{P}=(\text{Fo}^2 + 2\text{Fc}^2)/3$, were applied respectively. The reliability index is $\text{R}=0.034$, $\text{Rw}=0.083$ for L_6 and $\text{R}=0.096$, $\text{Rw}=0.26$ for L_4 . In L_4 the solvent methanol was refined isotropically. The analysis of the final different Fourier map does not reveal any useful information. The ORTEP plot was drawn using SHELXTL [14] and the geometrical parameters were calculated using PARST [15].

Results and discussion

Crystal structure of L_2

The crystal data of L_2 and L_4 are given in Table 3. Selected bond distance and angles of L_2 are given in Table 4. The ORTEP plot of the macrocycle is displayed in Fig. 1 together with the atomic labels. The bond distances and angles of the thiocyanate group are $\text{S} - \text{C}22=1.63(2)$; $\text{N}3 - \text{C}22 =1.20(2)$ Å and $\text{S} - \text{C}22 - \text{N}3=174.82^\circ$. The acetate group is above the plane of the diaza ring. All bond lengths and bond angles are within ranges of the reported values[16,17]. The protonation of the N atoms of the macrocycle is understood from the C-N bond distances (average C-N=1.499 Å) since the uncharged C-N distance is 1.467 Å. Similarly, the CO_2^- and the CO_2H groups are easily distinguished not only because of the location of the OH functions but also because the two C-O bonds are practically identical in the unprotonated moiety [$\text{C}17-\text{O}3=1.233(7)$ Å and $\text{C}17-\text{O}4=1.259(8)$ Å] whereas these bonds are different when a proton is attached. The O atoms are *cis* to each other with the twist of $-64.6(5)$ Å along C7-C8 bond. The torsion angles along the N-C-C-C-N chain are $70.1(4)$, $155.1(4)$, $-62.8(5)$, $-52.4(5)^\circ$. The N-acetate group lies perpendicular to the macrocyclic ring with the dihedral angle of $88.2(1)^\circ$ in order to avoid short contacts with the macrocycle so that it can

accommodate any guest molecule inside the cavity. In this ligand the O and N atoms lie in a plane with deviations 0.124(3); -0.137(3) for O and 0.123(3); -0.126(4) for N, respectively. A thiocyanate group, a methanol molecule and two water molecules present in the molecule do not contribute to the packing of the molecules. The 12-aza group (N2) of the ligand and the water molecule (O1W; $x-1,y,z$) forms an intermolecular hydrogen bonding [$N2-H2A=0.86(4)$; $N2 \cdots O1w=2.764(7)$; $N2-H2A \cdots O1w=112.7(4)^\circ$].

Crystal structure of L₄

Table 5 provides selected bond distances and angles of ligand L₆ and Fig.2 shows the ORTEP plot of the molecule with atomic numbering scheme. The O and N atoms of the macrocycle are the coordination sites of the ligand. The bond distances and angles are comparable with the reported values. The O-C-C-O chain can be described as *gauche-anti-gauche* conformation as evidenced by the values of the torsion angles. The tetrahedral distortion of the N₂O₂ donor system in the ligand is more significant as indicated by the deviations from the mean plane, 0.354(2), -0.401(2) for oxygen atoms O1 and O2 respectively and -0.257(2), 0.286(2) for nitrogen atoms N1 and N2 respectively. The two phenyl rings with atoms C1-C6 and C9-C14 lie nearly perpendicular to each other [dihedral angle $88.8(1)^\circ$], which indicates that quite a large folding is observed. For the protonated ligand of the same type, the corresponding value is reported as 48.8° . The maximum deviations are observed for the atoms C4 and C11 from the mean planes of the rings 1 and 2, respectively. The atom N3 of the macrocyclic ring and atom N4 of the ethanoamine group are *trans* to each other by making a torsion angle of $62.6(3)^\circ$ along C18-C19 bond.

The crystal structure is stabilized by intra- and inter- molecular hydrogen bonds. While one of the hydrogen of the water molecule is involved in forming the intra molecular hydrogen bonding with the bromine ion [O1W1-H2W1=1.059(3)Å; O1W1 ; -Br1= 3.458(3) Å and O1W1-H2W1 ; -Br1 = 137.7(2)°, the other forms the inter molecular hydrogen bonding with the bromine ion at $-x+1/2, +y-1/2, -z-1/2$ with the distance of 3.408(2)Å making an angle of 164.2(2)°. The aza nitrogen atoms N1 and N2 participate in intermolecular hydrogen bonds [N2-H2A=0.860(3); N2 ; -N1 (-x,-y+1, -z)=2.969(3)Å; N2 -H2A ; -N1 =103.8(2)° and N1-H1A=0.860(3); N1-N2=2.969(3) Å; N1-H1A ; -N2=104.3(2)°.

Protonation and stability constants

The protonation constants of these new ligands defined as stepwise proton association constants, the related parent macrocycles and the other analogous macrocycle N-substituted with acetate acids are summarized in table 1. There are three donor groups in ligand L₂: i.e. two basic nitrogen atoms from parent macrocycle and one oxygen atom from acetate acid. Constant K₁ refers to protonation constant of nitrogen atom substituted with acetate group; K₂ refers to protonation constant of another nitrogen atom of parent macrocycle; K₃ corresponds to protonation constant of acetate group. There are two donor groups of basic nitrogen atoms from the parent macrocycle in ligand L₄. The corresponding K₁ and K₂ refer to protonation constants of macrocyclic amine group. Nitrogen of cyanoethyl is too weakly basic to be protonated. For ligand L₆, K₁ refers to protonation constant of nitrogen atom substituted with ethylamine group, K₂ and K₃ refer to protonation constants of other amine group in the parent macrocycle, K₄ corresponds to protonation of first amine group. The basicity of tertiary amine is more

intense than that of second amine in parent macrocycle since substitution of function groups for hydrogen atoms increases the negative charge of the ligands. In these three ligands, their K_1 and K_2 corresponding to protonation at amine sites are different owing to different pendant arms of the ligands[5e]. The ether oxygen donors of the ligands are too weakly basic to be protonated.

The reaction of the ligands with transition metals Co, Ni, Cu, Zn, Cd has been studied in 95% ethanol solution [$I = 0.1$, Et_4NClO_4 , 25°C]. Stability constants of 1:1 complexes(molar ratio of metal and ligand) are listed in table 2.

For L_2 and L_6 , the set of the ethylamine and carbonyl arms in the macrocycle leads to equilibrium within a few minutes since the nitrogen of amine and the oxygen of carbonyl coordinate easily with metal ions. The results of elemental analysis and crystal structure confirm that the carboxyl and ethylamine arms participate in the formation of the complex. For L_2 , the observed log K values of complexes are considerably larger than that of the corresponding complex of the parent macrocycles, but slightly smaller than that of the complexes of L_3 , L_7 and L_8 , which shows the selectivity of L_2 is better than that of L_3 , L_7 and L_8 . For L_4 , the formation of coordination equilibrium is very slow since cyanoethyl in macrocycle restricts greatly the possible conformation on coordination to a metal ion. Also due to sterically hindered ligands, the stability of complexes are generally much lower than that of unsubstituted parent macrocycle [19]. The x-ray crystal structure and molecular model demonstrate that complexing capability of nitrogen atoms in cyanoethyl is too weak to participate in formation of complex [20].

For a same ligand, the formation constants of the bivalent metal ions follow the expected Irving-williams order: $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+}$. For a same metal ion, the order of the formation constants is $L_2 > L_6 > L_4$.

Crystal structures show that ether oxygen atoms of unsubstituted parent macrocycle participate in the formation of complexes in some of compounds [21], but they do not in other complexes [22]. Once a macrocycle with pendant arms, ether oxygen atoms in the macrocycle do not coordinate with metal ion owing to sterical effect[10,23]. These results confirm that ether oxygen atoms are less capable of binding than the amine nitrogen atoms in a same macrocyclic ligand.

Acknowledgment

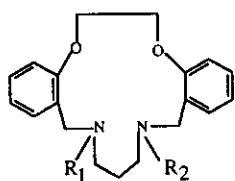
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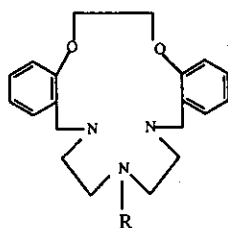


L₁ R₁ = R₂ = H

L₂ R₁ = H, R₂ = CH₂COOH

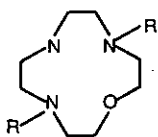
L₃ R = R = CH₂COOH

L₄ R₁ = R₂ = CH₂CH₂CN

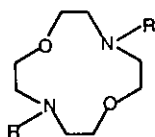


L₅ R = H

L₆ R = CH₂CH₂NH₂



L₇ R = CH₂COOH



L₈ R = CH₂COOH

Fig. 1 Scheme for Various Macrocycle Ligands with Various R Groups

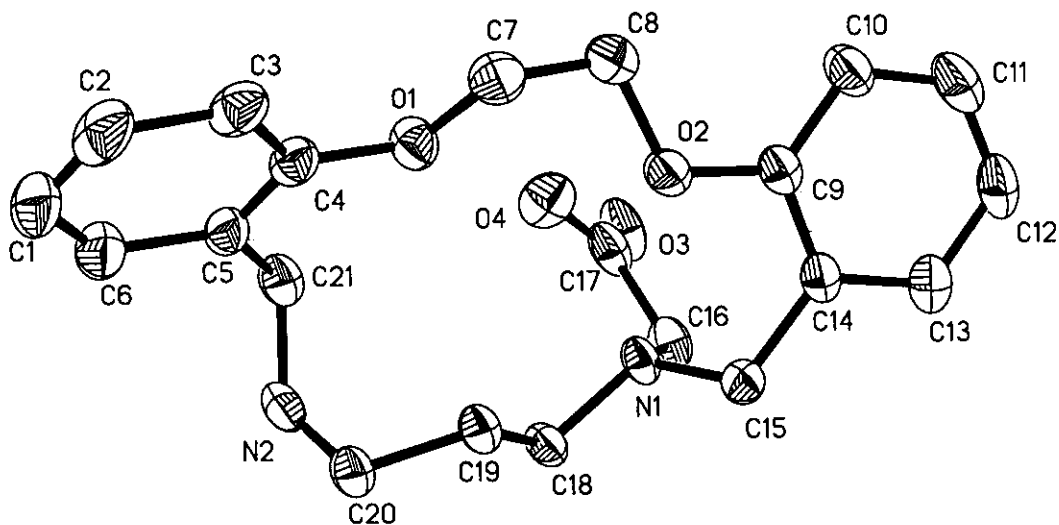


Fig.2. ORTEP plot of L₂ with atomic numbering scheme

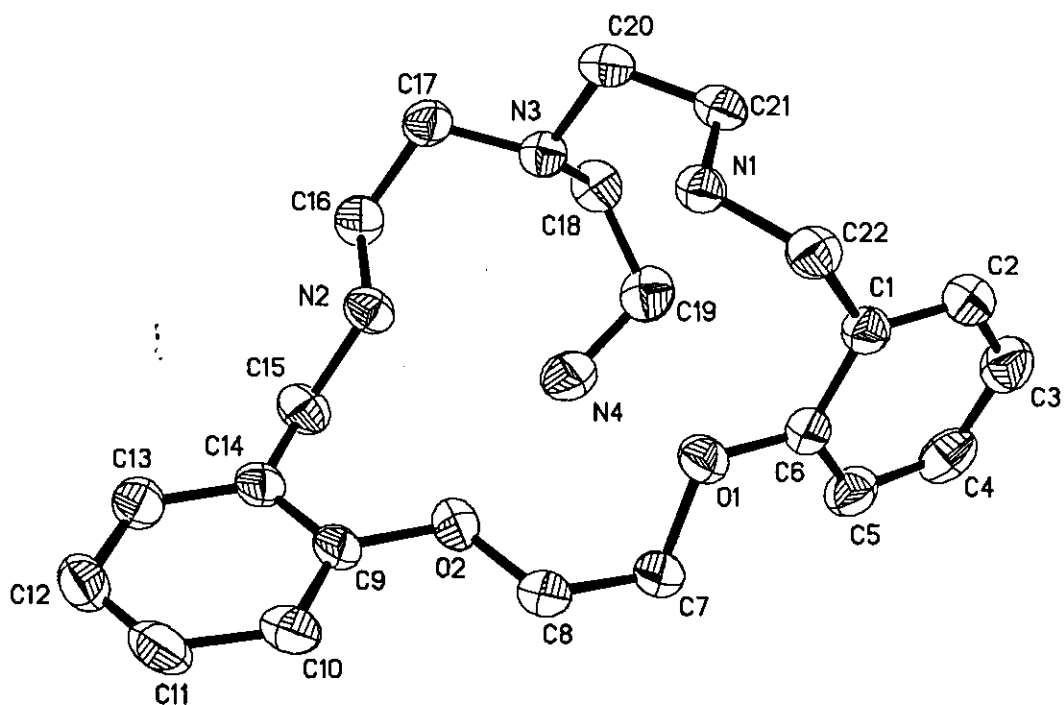


Fig.3. ORTEP plot of L_6 with atomic numbering scheme (Br ion and water molecule are omitted for clarity).

Table 1. Protonation constants of macrocyclic ligands N-substitute with various functional groups.

Ligand	$\log K_1$	$\log K_2$	$\log K_3$	$\log K_4$
L_1^{21a}	9.81	6.82		
L_2	10.38	7.51	1.98	
L_3^{5e}	10.45	7.85	1.96	
L_4	10.11	7.56		
L_5^{18}	9.47	8.27	2.35	
L_6	9.90	8.78	3.15	2.10
L_7^{5d}	11.24	6.02	2.94	
L_8^{5d}	9.55	7.46	2.1	

Table 2 Log K values for metal complex formation.

Ligand	Cu	Ni	Co	Cd	Zn
L ₁ ^{18,21}	7.2	5.4	< 4.5	4.1	
L ₂	13.8	9.5	6.8	8.2	7.9
L ₃ ^{5e}	14.9	9.9	7.6	8.4	8.3
L ₄	5.4	4.2	3.9	d	4.5
L ₅ ¹⁸	14.4(1)	10.0(1)	7.6(1)	8.7(1)	7.5(1)
L ₆	12.3	10.6	10.2	9.7	8.5
L ₇ ^{5d}	17.62	14.7	11.81	11.55	12.59

d) precipitation

Table 3. Crystal data and structure refinement for ligand L₂ and L₄.

	L ₄	L ₂
Empirical formula	C ₂₂ H ₃₅ BrN ₄ O ₃	C ₂₃ H ₂₅ N ₃ O ₇ S
Formula weight	483.45	487.52
Temperature(K)	296(2)	293(2)
Wavelength(Å)	0.71073	0.71073
Crystal system	P2(1)/n	P-1
Space group	monoclinic	triclinic
Unit cell dimensions		
a (Å)	11.5815(2)	8.6083(1)
b (Å)	10.6063(2)	11.9827(3)
c (Å)	19.4601(1)	12.8734(3)
α(°)	90	100.62(1)
β(°)	104.142(1)	92.360(2)
γ(°)	90	109.520(2)
Volume (Å ³)	2317.97(6)	1222.54(4)
Z	4	2
D _{cal} (mg/m ³)	1.385	1.324
μ(mm ⁻¹)	1.803	0.180
F(000)	1016	512
Crystal size(mm ³)	0.64 x 0.46 x 0.24	0.52 x 0.48 x 0.08
Colour	pale-yellow	bright yellow
θ range for data collection(°)	2.64 to 27.50	2.70 to 25.00
Reflections collected	15000	6561
Independent reflections	5293 [R(int) = 0.0247]	4186[R(int)=0.0235]
Refinement method	Full-matrix least-squares on F ²	Full-matrix least-squares on F ²
Data / restraints / parameters	5290 / 0 / 407	4186 / 0 / 297
Goodness-of-fit on F ²	1.017	1.059
Final R indices [I>2σ(I)]		
R	0.034	0.096
wR	0.0832	0.2608
Largest diff. peak and hole(e / Å ³)	0.475 and -0.531	0.728 and 0.614

Table 4. Selected bond lengths (Å) and bond angles (°) of L₂.

N1	C16	1.492(5)	N1	C15	1.505(5)		
N1	C18	1.508(5)	N2	C20	1.496(6)		
N2	C21	1.497(6)	O1	C4	1.376(5)		
O1	C7	1.425(6)	O2	C9	1.374(5)		
O2	C8	1.440(6)	O3	C17	1.233(6)		
O4	C17	1.259(6)	C4	C5	1.390(7)		
C5	C21	1.498(6)	C7	C8	1.482(7)		
C9	C14	1.392(6)	C14	C15	1.504(6)		
C16	C17	1.527(7)	C18	C19	1.532(6)		
C19	C20	1.521(6)	S	C22	1.63(2)		
N3	C22	1.20(2)	O5	C23	1.43(4)		
C16	N1	C15	114.6(3)	C16	N1	C18	111.9(3)
C15	N1	C18	113.8(3)	C20	N2	C21	116.7(3)
C4	O1	C7	118.1(3)	C9	O2	C8	117.6(3)
O1	C4	C5	115.5(4)	O1	C4	C3	123.1(4)
C4	C5	C21	122.5(4)	C6	C5	C21	120.3(5)
O1	C7	C8	109.8(4)	O2	C8	C7	109.3(4)
O2	C9	C10	125.2(4)	O2	C9	C14	114.5(4)
C9	C14	C15	119.7(4)	C13	C14	C15	120.7(4)
C14	C15	N1	109.3(3)	N1	C16	C17	109.0(4)
O3	C17	O4	126.5(5)	O3	C17	C16	118.0(5)
O4	C17	C16	115.4(4)	N1	C18	C19	109.7(3)
C20	C19	C18	113.3(4)	N2	C20	C19	114.5(3)
N2	C21	C5	112.5(4)	N3	C22	S	174.8(18)

Table 5. Selected bond lengths(Å) and bond angles(°) of L₄.

O1	C6	1.375(3)	O1	C7	1.435(3)		
O2	C9	1.373(3)	O2	C8	1.435(3)		
N1	C21	1.468(3)	N1	C22	1.473(3)		
N2	C16	1.486(3)	N2	C15	1.504(3)		
N3	C17	1.461(3)	N3	C20	1.468(3)		
N3	C18	1.475(3)	N4	C19	1.453(4)		
C1	C6	1.404(3)	C1	C22	1.515(3)		
C7	C8	1.486(4)	C9	C14	1.405(3)		
C14	C15	1.491(3)	C16	C17	1.522(3)		
C18	C19	1.519(4)	C20	C21	1.513(3)		
C6	O1	C7	116.8(2)	C9	O2	C8	117.1(2)
C21	N1	C22	114.1(2)	C16	N2	C15	112.3(2)
C17	N3	C20	111.6(2)	C17	N3	C18	112.5(2)
C20	N3	C18	111.9(2)	C2	C1	C6	117.9(2)
C2	C1	C22	121.9(2)	C6	C1	C22	120.2(2)
O1	C6	C5	123.8(2)	O1	C6	C1	115.4(2)
C5	C6	C1	120.8(2)	O1	C7	C8	108.8(2)
O2	C8	C7	108.3(2)	O2	C9	C10	123.9(2)
O2	C9	C14	115.5(2)	C13	C14	C9	118.0(2)
C13	C14	C15	119.6(2)	C9	C14	C15	122.4(2)
C14	C15	N2	113.8(2)	N2	C16	C17	110.0(2)
N3	C17	C16	111.5(2)	N3	C18	C19	113.1(2)
N4	C19	C18	111.2(2)	N3	C20	C21	112.6(2)
N1	C21	C20	110.2(2)	N1	C22	C1	115.4(2)