Complexes of Large Ring Macrocycles. The Preparation of the C-*meso*- and C-*racemic*-Diastereoisomers of Me$_6$[18]aneN$_4$ and Characterisation of their 'Blue' and 'Red' Copper (II) Complexes

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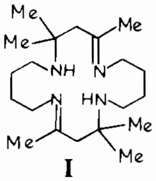
Abstract

The reaction of 1,4-diaminobutane monohydroperchlorate with acetone gives *trans*-Me$_6$[18]dieneN$_4$·2HClO$_4$·2H$_2$O. The diene can be reduced with NaBH$_4$ under basic conditions to give a mixture of C-*meso* Me$_6$[18]aneN$_4$ (melting point (m.p.) 119–120 °C) and C-*racemic* Me$_6$[18]aneN$_4$ (m.p. 79 °C) which can be separated by fractional crystallisation from xylene (Me$_6$[18]aneN$_4$ = 2,4,4,11,13,13-hexamethyl-1,5,10,14-tetraazacyclooctadecane). The free base form of Me$_6$[18]dieneN$_4$ has been characterised and molecular weight measurements by vapour pressure osmometry confirm the 18-membered tetraaza structure rather than the alternative 9-membered diaza structure. Blue copper(II) complexes [CuL](ClO$_4$)$_2$ have been characterised with both C-*meso* and C-*racemic* Me$_6$[18]aneN$_4$ which have a d–d band at 680 nm. These blue complexes are converted to the more thermodynamically stable red isomers (λ_{max} 488 nm) on stirring aqueous suspensions of the blue perchlorate salts. The red isomers are believed to have the *trans* III or *RSSR* configuration of the *sec*-NH centres.

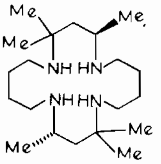
Introduction

Martell and coworkers [1] first synthesised Me$_6$[18]dieneN$_4$ (**I**) as the dihydroperchlorate salt by the reaction of 1,4-diaminobutane monohydroperchlorate with acetone. Copper(II) and nickel(II) complexes of the ligand were characterised and their structures determined by X-ray crystallography [2]. Complexes of the larger ring macrocycles are of interest as their complexes dissociate readily in acidic and basic solution. Such reactions have been studied kinetically for copper(II) and nickel(II) complexes of Me$_6$[18]dieneN$_4$ [3].



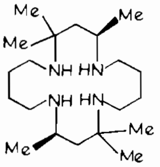
I

Initial attempts to reduce Me$_6$[18]dieneN$_4$* (dihydroperchlorate salt) or its copper(II) or nickel(II) complexes with BH$_4^-$ or H$_2$/Pd-charcoal in anhydrous methanol resulted in the breakdown of the macrocycle to 1,4-diaminobutane [1]. We have now found that the macrocycle can be reduced with NaBH$_4$ under basic conditions in methanol–water solvent to give good yields of the C-*meso* and C-*racemic* Me$_6$[18]aneN$_4$* ligands (**II** and **III** respectively) which can be separated by fractional crystallisation from xylene.



C-meso (L$_M$)

II



C-racemic (L$_R$)

III

The present paper describes the synthesis of these two new macrocyclic ligands and the characterisation of a number of copper(II) complexes.

Experimental

The macrocyclic ligand 2,4,4,11,13,13-hexamethyl-1,5,10,14-tetraazacyclooctadeca-1,10-diene dihydroperchlorate dihydrate H$_2$(*trans*-Me$_6$[18]dieneN$_4$)(ClO$_4$)$_2$·2H$_2$O was prepared essentially as previously described [3]. The yield using the quantities listed

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*Me$_6$[18]dieneN$_4$ = 2,4,4,11,13,13-hexamethyl-1,5,10,14-tetraazacyclooctadeca-1,10-diene; Me$_6$[18]aneN$_4$ = 2,4,4,11,13,13-hexamethyl-1,5,10,14-tetraazacyclooctadecane.

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was some 240 g. *Anal.* Calc. for $C_{20}H_{40}N_4 \cdot 2HClO_4 \cdot 2H_2O$: C, 41.89; H, 8.08; N, 9.77. Found: C, 42.06; H, 8.14; N, 9.75%. The ligand has a broad ν(OH) at 3500 cm^{-1}, ν(C=N) at 1665 cm^{-1} (sp) and ClO_4 bands at 1100 cm^{-1} (br) and 625 cm^{-1}.

Preparation of the Free Base Me$_6$[18]dieneN$_4$

The free base was prepared using the following procedure. A saturated solution of NaOH (*ca.* 100 cm^3, 16 M) was prepared with warm water. The ligand dihydroperchlorate dihydrate (*ca.* 10 g) was then added slowly with constant stirring. A yellow layer of the amine separated on the liquid surface and was twice extracted with $CHCl_3$ (300 cm^3). Removal of the $CHCl_3$ on a rotary evaporator gave the free amine as a yellow oil (*ca.* 3.5 g). The IR spectrum (liquid film) has a strong sharp band at 1665 cm^{-1} (ν(C=N)) and lacks the ClO_4^- bands at 1100 cm^{-1} and 625 cm^{-1}.

The molecular weight of the free amine was determined by vapour pressure osmometry using a Hewlett-Packard 302B Vapour Pressure Osmometer and toluene as solvent. Standardisation of the osmometer was carried out using toluene solutions of benzil. Five different concentrations were employed in each measurement. The molecular weight of the free base was found to be 320 ± 20 ($C_{20}H_{40}N_4$ = 336.57).

Reduction of H$_2$(trans-Me$_6$[18]dieneN$_4$)(ClO$_4$)$_2$·2H$_2$O with NaBH$_4$

Freshly prepared H_2(*trans*-Me$_6$[18]dieneN$_4$)-$(ClO_4)_2 \cdot 2H_2O$ was reduced with sodium borohydride as follows. The ligand dihydroperchlorate dihydrate (100 g, 0.17 mol) was dissolved in methanol–water (500 cm^3, 1:1 *v*/*v*). The solution was stirred, and $NaBH_4$ (19.3 g, excess) and NaOH (13.6 g, 0.34 mol) added in alternate small portions over a period of 4 h. The solution was cooled during the addition using a cold water bath. After completion of the addition, the solution was stirred for a further hour at room temperature, and then heated on a water bath for *ca.* 30 min, until the solution became clear. The solvent methanol was removed on a rotary evaporator, and the aqueous residue added to water (2 dm^3) and stirred for *ca.* 1 h. During this period the reduced ligand began depositing on the surface of the solution. The mixture was stored in a deep freeze overnight when the ligand deposited as a thick cake on the surface of the solution. The mixture of diastereoisomers was filtered off and dried *in vacuo*. Total yield 43 g.

Separation of Diastereoisomers

The mixture of diastereoisomers (43 g) was recrystallised from hot xylene (250 cm^3). On standing for several hours at room temperature, the *meso*-diastereoisomer slowly crystallised as beautiful small needles, and was filtered off. The filtrate contains the *racemic* diastereoisomer. The excess xylene was removed on a rotary evaporator to give the crude *racemic* diastereoisomer.

The *meso*-diastereoisomer was dissolved in the minimum volume of warm methanol and then poured into a beaker containing water (*ca.* 1 dm^3). On stirring for *ca.* 1 h and standing, the pure *meso* diastereoisomer deposited on the surface (this technique removes any xylene contamination). The *meso* diastereoisomer was dried *in vacuo*, m.p. 119 °C. The IR spectrum has ν(NH) at 3250 cm^{-1} (KBr disc). *Anal.* Calc. for $C_{20}H_{44}N_4$: C, 70.53; H, 13.02; N, 16.45. Found: C, 70.82; H, 13.06; N, 16.26%. The mass spectrum has $m/e^+ = 340.3557$, $C_{20}H_{44}N_4$ = 340.3566.

The *racemic* diastereoisomer was recrystallised from diethyl ether, m.p. 79 °C. The IR spectrum has ν(NH) at 3245 cm^{-1} (KBr disc). *Anal.* Calc. for $C_{20}H_{44}N_4$: C, 70.53; H, 13.02; N, 16.45. Found: C, 70.32; H, 13.05; N, 16.69%. The mass spectrum has $m/e^+ = 340.3557$, $C_{20}H_{44}N_4$ = 340.3566.

Preparation of Copper(II) Complexes

In the following procedures the nomenclature L_M is used for the C-*meso* diastereoisomer and L_R for the C-*racemic* diastereoisomer.

[CuL$_M$](ClO$_4$)$_2$

The ligand L_M (0.5 g, 0.0015 mol) was dissolved in methanol (15 cm^3) and added dropwise to a solution of copper(II) perchlorate hexahydrate (0.55 g, 0.0015 mol) in methanol (10 cm^3). The pale blue complex crystallised immediately. The complex was filtered off and recrystallised from a large volume of methanol. The compound is insoluble in cold water, methanol and ethanol. *Anal.* Calc. for $C_{20}H_{44}N_4Cl_2O_8Cu$: C, 39.83; H, 7.35; N, 9.29. Found: C, 39.98; H, 7.41; N, 9.16%.

[CuL$_M$](NO$_3$)$_2$

This complex was prepared as described above for the perchlorate salt, replacing copper(II) perchlorate hexahydrate with copper(II) nitrate hexahydrate (0.44 g, 0.0015 mol). The pale green complex formed immediately and was filtered off and recrystallised from a large volume of methanol. *Anal.* Calc. for $C_{20}H_{44}N_6O_6Cu$: C, 45.48; H, 8.40; N, 15.91. Found: C, 45.74; H, 8.49; N, 15.74%.

[CuL$_R$](ClO$_4$)$_2$

As for the C-*meso* analogue. The pale blue complex crystallised immediately and was filtered off and recrystallised from a large volume of methanol. *Anal.* Calc. for $C_{20}H_{44}N_4Cl_2O_8Cu$: C, 39.83; H, 7.35; N, 9.29. Found: C, 39.76; H, 7.43; N, 9.31%.

[CuL_M(red)](ClO_4)$_2$

A slurry of the pale blue [CuL_M]$(ClO_4)_2$ in warm water was stirred overnight. The undissolved material was filtered off and the red filtrate concentrated to give crystals of the red perchlorate salt. *Anal.* Calc. for $C_{20}H_{44}N_4Cl_2O_8Cu$: C, 39.83; H, 7.35; N, 9.29. Found: C, 39.65; H, 7.35; N, 9.20%.

A similar procedure was used to prepare [CuL_R(red)]$(ClO_4)_2$.

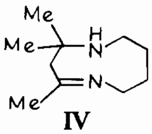
Measurements

Infrared spectra were determined as KBr discs or liquid films using a Perkin-Elmer 457 instrument. Electronic spectra were obtained with a Perkin-Elmer Lambda 5 instrument. The solid state spectra were determined as nujol mulls on filter paper. Mass spectra were obtained with a Jeol JMS D100 mass spectrometer.

Results and Discussion

The reaction of the monohydroperchlorate salts of α,ω-diamines with acetone in methanol solvent at −10 °C has provided a useful route for the synthesis of fourteen [4], eighteen [1, 3], twenty-two [5, 6] and twenty-six-membered [7] tetraaza macrocycles. The reaction presumably involves the Michael addition of the monohydroperchlorate salt of the diamine to mesityl oxide produced by base catalysed condensation of two moles of acetone, followed by diimine formation via condensation of the two β-amino ketone moieties. A possible mechanism has previously been outlined [8].

The analytical and ^{13}C NMR data do not differentiate between the 18-membered ring structure (**I**) and the possible 9-membered ring (**IV**). The formation of



IV

18-membered ring metal complexes could involve ring opening followed by cyclisation of the two 9-membered rings around the metal ion in a template reaction [1]. For this reason attempts were made to characterise the free base form of the ligand in order to carry out determinations of the molecular weight. The free base was readily isolated as described in the Experimental and molecular weight measurements by vapour pressure osmometry gave a value of M_R = 320 ± 20 (calc. for $C_{20}H_{40}N_4$ = 336.57) confirming the 18-membered ring structure **I**.

The reaction of monohydroperchlorate salts of α,ω-diamines with acetone or α,β-unsaturated ketones such as methyl vinyl ketone appears to be completely stereospecific giving the *trans*-diene with no evidence for formation of a *cis*-diene. In the case of **I** this conclusion has been verified by determination of the crystal structure of a copper(II) complex, [Cu(*trans*-Me_6[18]dieneN_4)]$(ClO_4)_2$ [2].

Although initial attempts to reduce H_2(*trans*-Me_6[18]dieneN_4)$(ClO_4)_2 \cdot 2H_2O$ were unsuccessful [1] we have found that the ligand can readily be reduced in methanol–water with $NaBH_4$ under basic conditions to give an approximately 50/50 mixture of the C-*meso* and C-*racemic* $Me_6[18]aneN_4$. The two diastereoisomers can readily be separated by fractional crystallisation from xylene.

The C-*meso* configuration is assigned to the diastereoisomer with m.p. 119–120 °C and the C-*racemic* configuration to the diastereoisomer m.p. 79 °C. A comparison of the melting points of C-*meso* and C-*racemic* diastereoisomers of similar macrocycles indicates that in every case the C-*meso* diastereoisomer has the higher melting point, Table I.

TABLE I. Melting Points of C-*meso* and C-*racemic* Diastereoisomers of Various Tetraaza Macrocycles

Macrocycle	Melting point (°C)	Reference
C-*meso*-Me_2cyclam	144.5–145	18
C-*rac*-Me_2cyclam	109.5–110	
C-*meso*-Et_2cyclam	139	19
C-*rac*-Et_2cyclam	104–110	
C-*meso*-Me_6cyclam(tet*a*)	146–147	8
C-*rac*-Me_6cyclam(tet*b*)	101–105	
C-*meso*-$Me_6[18]aneN_4$	119–120	This work
C-*rac*-$Me_6[18]aneN_4$	79	
C-*meso*-$Me_6[22]aneN_4$	128	5
C-*rac*-$Me_6[22]aneN_4$	75	

Copper(II) Complexes

A number of copper(II) complexes of the C-*meso* (L_M) and C-*racemic* (L_R) $Me_6[18]aneN_4$ were readily characterised including [CuL_M]$(ClO_4)_2$ (pale blue), [CuL_M]$(NO_3)_2$ (pale green) and [CuL_R]$(ClO_4)_2$ (pale blue). The complexes have very limited solubility in water, methanol, ethanol, dimethylsulphoxide and nitromethane. As a result, their electronic spectra were obtained using nujol mulls, Table II. Both complexes [CuL_M]$(ClO_4)_2$ and [CuL_R]$(ClO_4)_2$ display a broad d–d band at 680 nm with an intense charge transfer band at 296 nm. The position of the d–d band is similar to that observed in [Cutet*a*(blue)]$(ClO_4)_2$ (tet*a* = C-*meso* 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane) where λ_{max} 620 nm is observed [9]. This latter blue complex is converted to [Cutet*a*(red)]$^{2+}$ in slightly basic solution which has λ_{max} 520 nm. Similar behaviour is observed with the complexes [CuL_M]$(ClO_4)_2$ and [CuL_R]$(ClO_4)_2$. Stirring aqueous suspensions of the blue complexes gives red solutions which have λ_{max}

TABLE II. Spectral Characteristics of the Copper(II) Complexes of L_M and L_R

Complex	λ_{max} (nm)	IR (cm^{-1})
$[CuL_M](ClO_4)_2$(blue)	680^a 296^a	3220 (ν(NH))^b 3260 (ν(NH))
$[CuL_R](ClO_4)_2$(blue)	680^a 296^a	3220 (ν(NH))^b 3260 (ν(NH))
$[CuL_M](ClO_4)_2$(red)	488^c	
$[CuL_R](ClO_4)_2$(red)		

[a] Nujol mull spectra on filter paper. [b] Characteristic bands due to ionic perchlorate occur at 1100 cm^{-1} (br) and 620 cm^{-1}. [c] Aqueous solution.

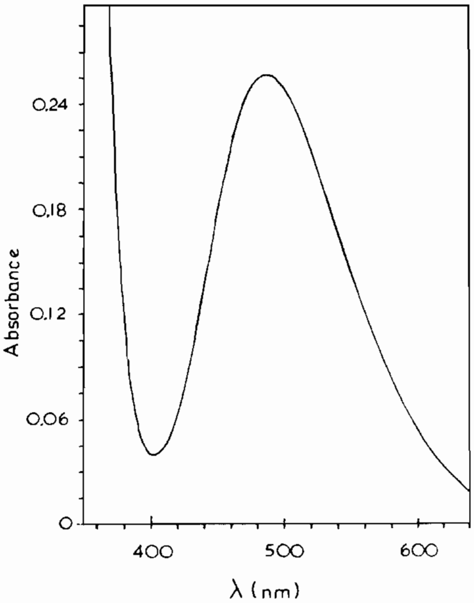
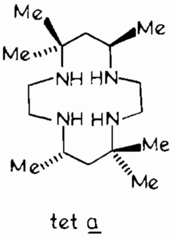


Fig. 1. Spectrum of $[CuL_M](ClO_4)_2$(red) in aqueous solution.

488 nm, Fig. 1. As with tet*a* (V) and tet*b* (VI) [10], copper(II) reacts with L_M and L_R to form initially a blue complex which is readily converted into the more thermodynamically stable red isomer. Such blue intermediates are not observed in the reaction of copper(II) with the less sterically hindered ligands such as cyclam and Me_2cyclam [11]. The blue $[Cu(tet\textit{b})]_2Cl(ClO_4)_3$ which contains 5-coordinate (trigonal-bipyramidal) copper with the tet*b* ligand folded has been characterised by X-ray crystallography [12]. Chloride ion, which occupies one of the positions in the trigonal plane dissociates from the copper in dilute solution, but the electronic spectral characteristics of the complex in aqueous solution are similar to those of the crystals [13]. The blue complex is the kinetically controlled product, and is readily converted to the more thermodynamically stable red isomer in basic solution [14, 15]. The tet*b* ligand is known to readily fold to give *cis*-complexes with the *RRRR*(*SSSS*)*sec*-NH configuration, while tet*a* only folds with difficulty. The crystal structures of the blue and red complexes of $[Cu(tet\textit{a})]^{2+}$ have been described [16].



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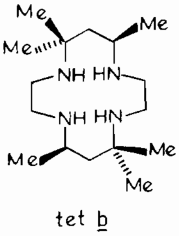
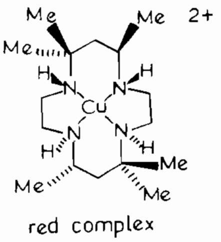
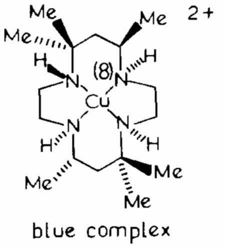


VI

The complex $[Cu(tet\textit{a})(red)](ClO_4)_2$ contains tetragonally distorted copper(II) with monodentate perchlorate in the axial sites. The macrocyclic ligand occupies the equatorial plane with the *sec*-NH configuration shown in **VII**. The essential difference between the structures of the red and blue complexes is the inversion of the *sec*-NH group at N(8) (**VIII**).



VII



VIII

This small change in geometry causes dramatic spectral changes with λ_{max} for the blue diastereoisomer occurring at 636 nm ($\epsilon = 174$ M^{-1} cm^{-1}), while the red diastereoisomer has λ_{max} 515 nm ($\epsilon = 146$ M^{-1} cm^{-1}) in water solvent. Similar dramatic spectral changes occur with the present complexes with the blue complexes having λ_{max} at 680 nm in the solid state, Table II, while the red species have λ_{max} 488 nm in aqueous solution, Fig. 1. One noteworthy feature of the infrared spectra of the blue complexes is that they display two ν(NH) bands at 3220 and 3260 cm^{-1} KBr disc) which may be indicative of a folded configuration for the macrocycle. In no case where a tetraaza macrocycle is known to be folded, so that the four donor nitrogen atoms occupy *cis*-positions has a single N–H stretching frequency been reported [17]. It is likely that the red complexes have the most thermodynamically stable *trans* III or *RSSR* configuration of the *sec*-NH centres, but the structures of the blue species must remain speculative until crystal structure analyses have been carried out.

The blue complexes are quite labile in acid, undergoing ready dissociation. As a result of the very limited water solubility of the blue perchlorate salts,

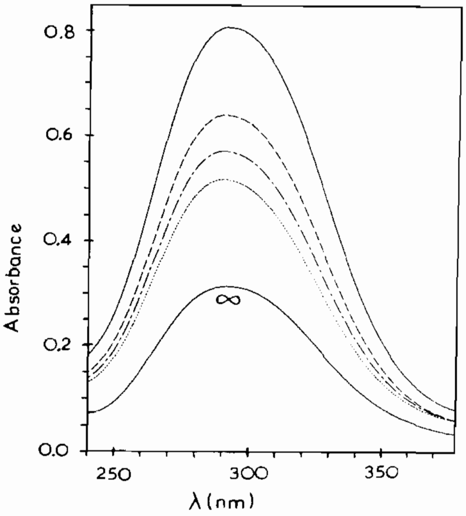


Fig. 2. Spectral changes observed at the charge transfer band for the dissociation of $[CuL_M](ClO_4)_2$(blue). Temperature 25 °C with $[HClO_4] = 0.1$ M. The time interval between scans is 8 min, the infinity spectrum was obtained after 24 h.

it was necessary to monitor the dissociation at the charge transfer band, 296 nm. Figure 2 illustrates the spectral changes occurring with $[CuL_M](ClO_4)_2$ in 0.1 M $HClO_4$ at 25 °C. The half life of the reaction under these conditions is *ca.* 17 minutes.

Acknowledgements

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