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Complexes of Large Ring Macrocycles. The Preparation of $Me_6[22]dieneN_4$, C-*meso* $Me_6[22]aneN_4$, C-*racemic* $Me_6[22]aneN_4$ and some Binuclear Copper(II) and Nickel(II) Complexes

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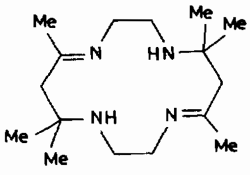
Abstract

The reaction of 1,6-diaminohexane monohydroperchlorate with acetone gives $Me_6[22]dieneN_4 \cdot 2HClO_4$† in high yield (*ca.* 85%). Reduction of the diene with $NaBH_4$ in methanol gives a mixture of C-*meso* $Me_6[22]aneN_4$†† (m.p. 128 °C) and C-*racemic* $Me_6[22]aneN_4$ (m.p. 75 °C) which can be separated by fractional crystallisation from hot xylene. The free base form of $Me_6[22]dieneN_4$ has been characterised and molecular weight measurements by vapour pressure osmometry confirm the 22-membered ring structure.

The ligands give binuclear methoxy-bridged complexes of the type $[M_2L(OCH_3)_2](ClO_4)_2$ with metal ions such as copper(II) and nickel(II) L = C-*meso* $Me_6[22]aneN_4$ or $Me_6[22]dieneN_4$).



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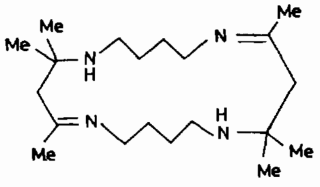

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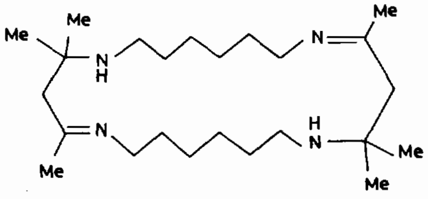

III

Introduction

The preparation of $Me_6[14]dieneN_4$ (I) as its monohydroperchlorate salt, by the reaction of ethylenediamine monohydroperchlorate with acetone was first developed by Curtis and Hay [1].

Subsequent work has shown that larger rings can also be prepared if other α,ω-diamines are employed in the reaction. Thus Martell and coworkers [2] have synthesized $Me_6[18]dieneN_4$ (II) by the reaction of 1,4-diaminobutane monohydroperchlorate with acetone. Very recently Yamashita, Ito and Ito [3] have prepared $Me_6[22]dieneN_4$ (III) as its dihydroperchlorate salt by reaction of 1,6-diaminohexane with acetone. Reduction of $Me_6[22]dieneN_4 \cdot 2HClO_4$ with $NaBH_4$ gives a mixture of C-*meso* and C-*racemic* $Me_6[22]aneN_4$. The C-*meso* diastereoisomer reacts with $Cu(ClO_4)_2 \cdot 6H_2O$ in methanol to give $[Cu_2(Me_6[22]aneN_4)(OCH_3)_2](ClO_4)_2$. The copper ions are 4-coordinate with two N atoms of the macrocycle and two O atoms of the alkoxo ligands acting as donors. The Cu---Cu separation is 3.034 Å with a Cu–O–Cu angle of 102.50°. There is a relatively strong antiferromagnetic interaction between the Cu(II) ions with magnetic moments of 0.87 B.M. at 299 K and 0.19 B.M. at 81 K.

Binuclear copper complexes have received considerable attention in recent years as models for Type III copper sites in metalloproteins [4]. The synthesis of macrocyclic dicopper(II) complexes have been reported by a number of groups [5–9] and the topic has been recently reviewed [10]. The present paper discusses the synthesis of $Me_6[22]dieneN_4$ and its reduction products C-*meso* and C-*racemic* $Me_6[22]aneN_4$. A variety of alkoxy-bridged copper(II) and nickel(II) complexes of $Me_6[22]dieneN_4$ and C-*meso* $Me_6[22]aneN_4$ have been characterised.

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†$Me_6[22]dieneN_4$ = 2,2,4,13,13,15-hexamethyl-1,5,12,16-tetraazacyclodocosa-4,15-diene.

††$Me_6[22]aneN_4$ = 2,2,4,13,13,15-hexamethyl-1,5,12,16-tetraazacyclodocosane.

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Experimental

The macrocyclic ligand Me_6[22]dieneN_4·2HClO$_4$ was prepared using the following procedure. Perchloric acid (72%, 83 cm^3, 1 mol) was added dropwise with continuous stirring to a cooled (ice-salt bath) solution of 1,6-diaminohexane (116.2 g, 1 mol) in methanol (400 cm^3). The perchloric acid was added at such a rate that the temperature of the reaction mixture was always less than –10 °C. After completion of the addition, acetone (117 cm^3, 2 mol) diluted with methanol (80 cm^3) was added dropwise over a period of three hours. During this time the temperature was maintained at *ca.* 5 °C. After completion of the addition the solution was stirred for 5 to 6 h at 0–5 °C. During this period the solution developed a faint pale yellow colour. The solution was refrigerated for 4–5 days when colourless crystals of the dihydroperchlorate salt slowly deposited. The yield is *ca.* 85%. The ligand salt is unstable at room temperature and gradually becomes brown and decomposes. The compound can be stored in a deep freeze where decomposition is slow. (Caution! Great care should be exercised with amine hydroperchlorate salts as they can detonate with great violence on heating.) *Anal.* Calcd. for $C_{24}H_{50}N_4Cl_2O_8$, C, 48.56; H, 8.49; N, 9.44. Found: C, 48.52; H, 8.76; N, 9.44%. The ligand dihydroperchlorate has a strong ν C=N at 1660 cm^{-1} and ClO_4^- bands at 1100 cm^{-1} (br) and 625 cm^{-1}.

Preparation of the Free Base Me_6[22]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 (*ca.* 10 g) was then added slowly with constant stirring. A thick 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 rotatory evaporator gave the free amine as an oil. The IR spectrum (thin film) has a strong band at 1660 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 386 ± 8 ($C_{24}H_{50}N_4$ requires 394.7).

Reduction of Me_6[22]dieneN_4·2HClO$_4$ with NaBH$_4$

Freshly prepared Me_6[22]dieneN_4·2HClO$_4$ was reduced with sodium borohydride as follows. The ligand dihydroperchlorate (50 g, 0.084 mol) was added to methanol (200 cm^3) in a 1-litre beaker. The beaker was placed in an ice bath and $NaBH_4$ (9.25 g) added in small portions over a period of four hours, with continuous stirring. Stirring was continued for *ca.* 5–6 h after completion of the addition, and methanol was added as required to maintain the solution volume. The mixture was then heated on a water bath for 15–20 minutes to give a clear solution. The solution was cooled and sodium hydroxide solution (3 M) added to make the solution highly basic (pH *ca.* 12). Some 60–70% of the methanol was removed on a rotatory evaporator and the residue added to a large volume of water. The mixture was stirred with a mechanical stirrer for about 1 h, during which 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 ligand may be contaminated by some $NaClO_4$ at this stage. To remove any $NaClO_4$, the ligand was dissolved in the minimum volume of ethanol which was then added to a large volume of water. On standing the mixture of C-*meso* and C-*racemic* Me_6[22]aneN_4 (*ca.* 60% *meso* and 40% *racemic*) deposited. Total yield *ca.* 26 g (*ca.* 50%).

Separation of Diastereoisomers

The *meso* diastereoisomer was obtained by fractional crystallisation from hot xylene. The *meso* isomer is less soluble than the *racemic* isomer in xylene. A hot solution of the diastereoisomers in xylene slowly deposits, at room temperature, small needle-shaped colourless crystals of the pure *meso* diastereoisomer m.p. 128 °C. The IR spectrum has ν NH at 3250 cm^{-1} (KBr disc). *Anal.* Calcd. for $C_{24}H_{52}N_4$: C, 72.67; H, 13.21; N, 14.12. Found: C, 72.24; H, 13.55; N, 14.15%. The ^{13}C NMR spectrum in $CDCl_3$ gives the expected 12 lines due to the pairwise equivalence of the carbon atoms. ^{13}C NMR ($CDCl_3$, 25 MHz, δ): 21.6; 25.6; 28.4; 29.0; 30.9; 31.3; 42.1; 48.0; 48.6; 51.6; 52.9. The mass spectrum has m/e$^+$ = 396.4193, $C_{24}H_{52}N_4$ = 396.4192.

The C-*racemic* diastereoisomer was recrystallised from diethyl ether, m.p. 75 °C. The IR spectrum has ν NH at 3245 cm^{-1} (KBr disc). *Anal.* Calcd. for $C_{24}H_{52}N_4$: C, 72.67; H, 13.21; N, 14.12. Found: C, 72.26; H, 13.1; N, 14.22%. The ^{13}C NMR spectrum has 12 signals due to pairwise equivalence of the carbon atoms. ^{13}C NMR ($CDCl_3$, 25 MHz, δ): 21.5; 26.1; 28.3; 29.1; 30.8; 31.2; 42.0; 47.8; 48.1; 48.6; 51.7; 52.9. The mass spectrum has m/e$^+$ = 396.4183, $C_{24}H_{52}N_4$ = 396.4192.

Preparation of Binuclear Metal Complexes

[Cu_2(Me_6[22]diene)(OCH_3)$_2$](ClO_4)

Freshly prepared Me_6[22]diene·2HClO$_4$ (1 g, 1.67 mmol) was dissolved in dry methanol (25 cm^3).

The ligand solution was then added dropwise with stirring to copper(II) acetate monohydrate (0.66 g, 3.34 mmol) dissolved in the minimum volume of hot dry methanol. The solution gradually became deep violet, and on completion of the addition was stirred for *ca.* 1 h at room temperature. Dry ethanol (*ca.* 4 cm^3) was added and the solution refrigerated (in a sealed flask) for about 1 week. During this time violet fibre-like crystals deposited. The complex was recrystallised from the minimum quantity of hot methanol. The IR spectrum (KBr disc) has ν C=N at 1660 cm^{-1} and ClO_4^- bands at 1100 and 625 cm^{-1}. *Anal.* Calcd. for $C_{26}H_{54}N_4O_{10}Cl_2Cu_2$: C, 40.00; H, 6.97; N, 7.18. Found: C, 39.84; H, 7.05; N, 7.47%.

$[Ni_2(C\text{-}meso\ Me_6[22]aneN_4)(OCH_3)_2](ClO_4)_2$

Methanol dried by refluxing and distilling over magnesium methoxide was used in this preparation. The C-*meso* ligand (0.2 g, 0.5 mmol) was dissolved in dry methanol (15 cm^3) and 2,2-dimethoxypropane (2 cm^3) added. The solution was refluxed for *ca.* 1 h to remove water. Nickel(II) perchlorate hexahydrate (0.36 g, 1 mmol) was dissolved in hot methanol (10 cm^3) and 2,2-dimethoxypropane (2 cm^3) added. The solution was then refluxed for *ca.* 1 h. When the two solutions were mixed at room temperature with stirring, a pale green complex precipitated. The complex was recrystallised from hot dry methanol. *Anal.* Calcd. for $C_{26}H_{58}N_4O_{10}Cl_2Ni_2$: C, 40.29; H, 7.54; N, 7.23. Found: C, 40.33; H, 7.50; N, 6.98%. The IR spectrum (KBr disc) has the characteristic bands due to ionic perchlorate at 1100 cm^{-1} and 625 cm^{-1}.

$[Cu_2(C\text{-}meso\ Me_6[22]aneN_4)(OCH_3)_2](ClO_4)_2$

This complex was prepared as for the nickel(II) derivative using $Cu(ClO_4)_2 \cdot 6H_2O$. The blue-green complex was recrystallised from hot methanol. *Anal.* Calcd. for $C_{26}H_{58}N_4O_{10}Cl_2Cu_2$: C, 39.79; H, 7.45; N, 7.14. Found: C, 39.25; H, 7.64; N, 7.32%.

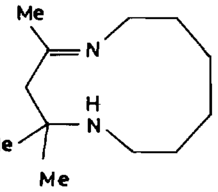
$[Cu_2(C\text{-}meso\ Me_6[22]aneN_4)(OC_2H_5)_2](ClO_4)_2$

The C-*meso* ligand (0.2 g, 5 × 10^{-4} mol) was dissolved in dry ethanol (15 cm^3) and 2,2-dimethoxypropane (1 cm^3) added. The solution was refluxed for *ca.* 0.5 h for complete dehydration and allowed to cool. Copper(II) perchlorate 6-hydrate (0.37 g, 1 × 10^{-3} mol) was dissolved in ethanol (20 cm^3) and refluxed with 2,2-dimethoxypropane (1 cm^3) for 30 min. The solution was filtered and slowly added to the solution of the ligand. A blue-green precipitate immediately formed. The complex was filtered off and recrystallised from hot ethanol. *Anal.* Calcd. for $C_{28}H_{62}N_4Cl_2O_{10}Cu_2$: C, 41.37; H, 7.69; N, 6.89. Found: C, 41.54; H, 7.57; N, 7.04%.

Infra-red spectra were determined as KBr discs with a Perkin Elmer 457 instrument. Electronic spectra were obtained with a Perkin Elmer 402 instrument. The solid state spectra were determined as nujol mulls on filter paper; solution spectra were obtained using DMF as solvent. The ^{13}C NMR spectra were obtained with a Bruker WP80 instrument and the mass spectra with a Jeol JMS D100 mass spectrometer.

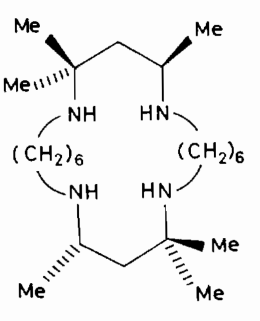
Results and Discussion

The reaction of 1,6-diaminohexane monohydroperchlorate with acetone in methanol at −10 °C gives excellent yields (*ca.* 85%) of H_2(*trans*-Me$_6$-[22]dieneN$_4$)(ClO$_4$)$_2$ (the dihydroperchlorate salt of 2,2,4,13,13,15-hexamethyl-1,5,12,16-tetraazacyclodocosa-4,15-diene). The reaction presumably involves the Michael addition of the monohydroperchlorate salt of 1,6-diaminohexane to mesityl oxide produced by base catalysed condensation of two mol of acetone, followed by diimine formation via condensation of the two β-amino ketone moieties. The mechanism has previously been outlined [1, 11]. Reactions of this type appear to proceed stereospecifically giving the *trans*-diene-(III) with no evidence for formation of the *cis*-diene. The analytical and ^{13}C NMR data do not differentiate between the 22-membered ring structure (III) and the possible 11-membered ring (IV). The formation of 22-membered ring metal complexes could involve metal ion promoted ring opening and cyclisation of two 11-membered rings. For this reason, attempts were made to characterise the free base form of the ligand for molecular weight measurements. The free base is readily isolated as described in the Experimental and molecular weight measurements by vapour pressure osmometry gave a value of M = 386 ± 8 (calc. for $C_{24}H_{50}N_4$, M = 394.7) confirming the 22-membered ring structure (III).



IV

The *trans*-diene ligand is readily reduced by NaBH$_4$ in methanol to give an approximately 60/40 mixture of C-*meso* and C-*racemic* Me$_6$[22]aneN$_4$ (C-*meso* and C-*racemic* 2,2,4,13,13,15-hexamethyl-1,5,12,16-tetraazacyclodocosane) respectively. The two diastereoisomers can readily be separated by fractional crystallisation from xylene. The C-*meso* diastereoisomer (**V**) (m.p. 128 °C) is less soluble in xylene than the C-*racemic* diastereoisomer (**VI**) (m.p. 75 °C). The latter amine can be purified by crystallisation from diethyl ether.



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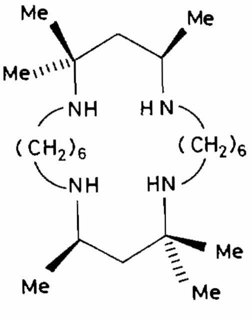
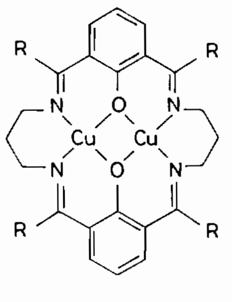


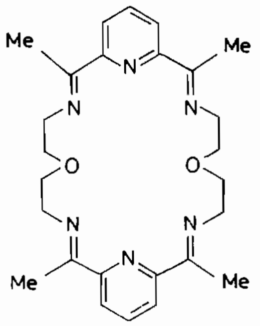
VI

Binuclear Metal Complexes

The 22-membered macrocycles $Me_6[22]dieneN_4$ and C-*meso* $Me_6[22]aneN_4$ are sufficiently large to incorporate two copper(II) or nickel(II) ions to give binuclear complexes. Binuclear copper(II) complexes of 20-membered (**VII**) [7] and 24-membered (**VIII**) [5] macrocycles have previously been characterised.



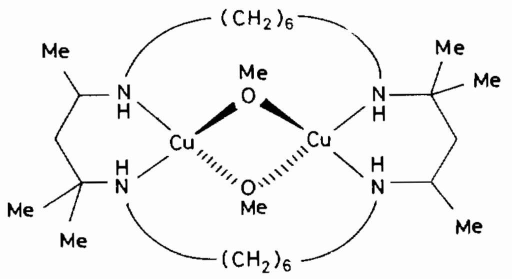
VII



VIII

Previous X-ray work [3] has established that $[Cu_2(C\text{-}meso\ Me_6[22]aneN_4)(OCH_3)_2](ClO_4)_2$ has the structure (**IX**). Each copper is coordinated to two N atoms of the macrocycle and two O atoms of the alkoxo groups, the dihedral angle between the NCuN and OCuO planes being 36.6 °C. The two copper ions and the four N atoms are coplanar, and the Cu---Cu separation is 3.034 Å with a Cu–O–Cu angle of 102.5°.

In various hydroxo-bridged dicopper(II) complexes it has been observed [12–14] that the ground state is a triplet if the Cu–O–Cu bridge angle is less than 97.6°, and a singlet if the angle is greater than 97.6°. This observation has been rationalised theoretically [12, 13, 15] on the basis of the super-



IX

exchange principle [16] involving a pathway for spin coupling of the two unpaired electrons in $d_{x^2-y^2}$ orbitals of each copper(II) and s and p orbitals of the bridging oxygen. Relatively strong antiferromagnetic interaction between the copper centres is expected and thus the magnetic moment of $[Cu_2(C\text{-}meso\ Me_6[22]aneN_4)(OCH_3)_2](ClO_4)_2$ is 0.87 BM at 299 K and no ESR signal is observed in DMF solution at liquid nitrogen temperatures [3].

The solid state spectrum (nujol mull) of $[Cu_2(C\text{-}meso\text{-}Me_6[22]aneN_4)(OCH_3)_2](ClO_4)_2$ has absorption bands at 722 nm, 604 nm and 393 nm, Table I. Although the complex has very limited solubility in DMF, the following solution spectrum has been reported 730 nm (ε = 340), 602 nm (ε = 320) and 393 nm (ε = 2200 M^{-1} cm^{-1}) [3]. An almost identical solid state spectrum is given by the ethoxy bridged derivative with bands at 720 nm, 606 nm and 390 nm. The two lower energy bands are assigned to d–d transitions. Binuclear copper(II) complexes with the $N_2CuO_2CuN_2$ type of chromophore have been shown to have a characteristic band in the

TABLE I. Electronic Spectra of the Binuclear Complexes.

Complex	max (nm)	M^{-1} cm^{-1}
$[Cu_2(L^1)(OMe)_2](ClO_4)_2$	722^a (730)^c	(340)
	604 (602)	(320)
	393 (393)	(2200)
$[Cu_2(L^1)(OEt)_2](ClO_4)_2$	720^a	–
	606	–
	390	–
$[Cu_2(L^2)(OMe)_2](ClO_4)_2$	578^b	158
	350sh	1960
	300	7450
$[Ni_2(L^1)(OMe)_2](ClO_4)_2$	660^a	–
	395	–

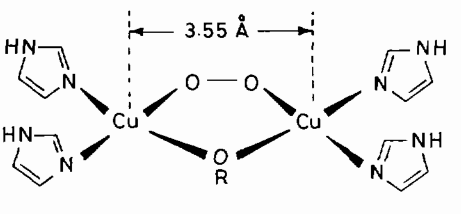
^{a}Nujol mull spectra. ^{b}Solution spectra in DMF solvent. L^1 = C-*meso* $Me_6[22]aneN_4$; L^2 = $Me_6[22]dieneN_4$. ^{c}Values in parenthesis apply to the solution spectrum determined in DMF (Ref. 3).

345–415 nm region assigned to a $p\pi(O) \rightarrow d_{x^2-y^2}$(Cu) transition [17] leading to the band at 393 nm. A somewhat similar spectrum is observed with $[Cu_2(Me_6[22]dieneN_4)(OCH_3)_2](ClO_4)_2$, but in this case presumably as a result of the stronger ligand field exerted by the imine donors, the lowest energy d–d band moves to 578 nm, with a strong shoulder at 350 nm ($\epsilon \sim 1960\ M^{-1}\ cm^{-1}$) assigned to the O → Cu(II) charge transfer absorption.

The nickel(II) complex $[Ni_2(C\text{-}meso\ Me_6[22]aneN_4(OCH_3)_2](ClO_4)_2$ is pale green in colour, typical of an octahedral species. The IR spectrum shows no evidence for water and thermogravimetric measurements established that the weight loss at 100 °C was *ca.* 2% (monohydrate = 2.27%). The solid state spectrum (nujol mull) has bands at 15,150 cm^{-1} and 25,300 cm^{-1} which can be assigned to the $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ and the $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ transitions respectively in O_h. The NiO_4N_2 chromophore normally gives bands at 15,500 and 25,000 cm^{-1} for these transitions [18]. It is probable that perchlorate anions occupy axial sites leading to a pseudo octahedral stereochemistry on nickel [19].

Attempts to isolate complexes of the C-*racemic* ligand have not been successful and this agrees with a preliminary report [3] that reaction of $Cu(ClO_4)_2 \cdot 6H_2O$ with a mixture of the C-*meso* and C-*racemic* ligands gave only $[Cu_2(meso\text{-}Me_6[22]aneN_4)(OCH_3)_2](ClO_4)_2$ with the recovered free ligand being the C-*racemic* diastereoisomer.

In spite of the non-biological nature of the macrocyclic ligand, the binuclear copper complexes provide a useful structural model for the oxidised (ESR silent) haemocyanin active site. Oxyhaemocyanin contains two copper(II) atoms in approximately square planar environments. Both coppers are coordinated to two histidines and two oxygen atoms, one of which is from a peroxo-bridging ligand and the other is believed to be the phenolic oxygen of a tyrosine residue of the protein (X) [20, 21]. The Cu–Cu distance of 3.55 Å compares with 3.03 Å in the present methoxy-bridged complexes.



X

Acknowledgment

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