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SYNTHESIS OF OPTICALLY ACTIVE DIAMINO-DIIMINE MACROCYCLE (6S,15S)-1,5,10,14-TETRAAZA-4,13-DIMETHYL-TRICYCLO[13.3.1.1^{6,10}]ICOSA-4,13-DIENE AND MOLECULAR STRUCTURE OF ITS NICKEL(II) COMPLEX

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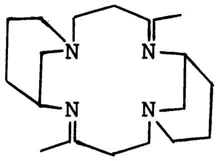
An optically active tetra-aza macrocycle was prepared by a simple method, employing an optically active N-substituted diamine as a starting material, and the molecular structure of its nickel(II) complex was determined by an X-ray crystallographic analysis.

The synthesis of macrocyclic compounds, especially the optically active macrocycles, is generally quite laborious, and the yield is usually very low. However, it was shown in previous papers$^{1,2)}$ that the copper(II) complexes of optically active macrocycles, (**1**) the compound in the title, and (6S,16S)-1,5,11,15-tetraaza-4,14-dimethyl-tricyclo[14.4.1.1^{6,11}]docosa-4,14-diene (**2**) could be obtained by a reaction of copper(II) complex of the corresponding optically active diamines, (3S)-3-aminopiperidine (**3**) and (3S)-3-aminohexahydroazepine (**4**), with 3-buten-2-one. The reaction with **3** proceeded smoothly to give **1** in a yield of ca. 80%. Such template reaction was, however, applicable only to the synthesis of copper(II) complexes. In this communication, we wish to report the synthesis of optically active macrocyclic ligand **1** through a non-template reaction, and metal ion insertion reaction into **1**, giving complexes with a few metal ions. The results of the structural determination performed on the nickel(II) complex of **1** by single crystal X-ray diffraction analysis, are also presented, and revealed the interesting stereochemical feature of this complex.



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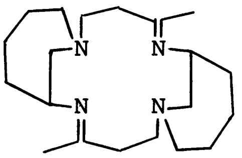

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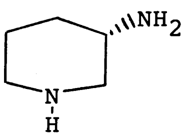

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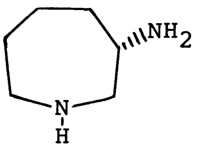

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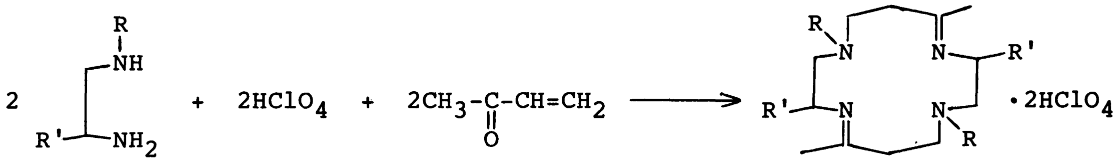
Thus the diamine **3**, which has both N- and C-substituents linked to form the heterocycle, was neutralized with an equimolar amount of $HClO_4$(60%), and the mono(hydroperchlorate) of **3** was allowed to react with 3-buten-2-one in methanol at ice bath temperature. A colourless precipitate which formed was assigned to the di(hydroperchlorate) of **1** on the basis of the infra-red spectral and the elemental analysis data (Scheme 1-(a)).[3] The yield of the product was ca. 40%.

Although this type of reaction has been reported for obtaining a tetra-aza macrocycle from 1,2-diaminoethane (Scheme 1-(b)),[4,5] the reaction with N-substituted diamines has never been reported. Whether the Michael addition, which forms the C-N bond on the β-position of 3-buten-2-one, proceeds at the primary or secondary amino group of the diamine decides the reaction path to produce either a linear ligand or a macrocyclic. The result indicates that at least 40% of the Michael addition occurs at the secondary amino group and that the introduction of N-substituents into a macrocycle can be achieved merely by using N-substituted diamines as the starting compound. The introduction of N-substituents is known as effective for restricting the conformation of the ligands by preventing the inversion of chiral N-centres.[6,7] Further, it must be noted that the N-substituents are always introduced at the opposite side of the linked four nitrogen atoms (i.e. in trans position).



Scheme 1. Formation of diamino-diimine tetra-aza macrocycles:
(a) $R+R'=-CH_2CH_2CH_2-$, (b) $R=R'=H$.

The di(hydroperchlorate) of macrocycle **1** reacted with the acetates of nickel(II), copper(II), and cobalt(II) in ethanol to afford the di(perchlorate) of metal complexes. The nickel(II) and copper(II) complexes show the electronic spectra typical of the square planar coordination.[8] The infra-red and electronic spectra of the copper(II) complex are identical with those of the complex obtained from the template reaction.[2] The nickel(II) complex exhibited a clear ^1H NMR spectrum in D_2O,[9] which indicates that this complex is diamagnetic and takes a square planar geometry. The spectral pattern shows the presence of C_2 symmetry as has been predicted.

The molecular structure of nickel(II) complex of **1** in the di(perchlorate) salt was investigated by a single-crystal X-ray analysis. The prismatic, orange crystal (0.40x0.40x0.48 mm^3) was obtained from an aqueous solution of $[Ni(\mathbf{1})](ClO_4)_2$, and used as a sample for X-ray analysis. Intensity data were collected on a Rigaku AFC-5 automated four-circle diffractometer with graphite-monochromatized Mo Kα radiation (λ=0.71073 Å) and by using ω and ω-2θ (2θ>30°) scan method with the scan rate of 4.0°/min. Four standard reflections were measured after every 150 reflections. Intensities were corrected for Lorentz and polarization factors, but not for absorption. Details of the experimental conditions are listed in Table 1. The structure was solved by the direct method, and were refined by the block-diagonal least-squares technique. These crystallographic calculations were performed on a FACOM M-380 computor using the UNICS III program system[10] and MULTAN 78.[11] All non-hydrogen atoms are treated as anisotropic and hydrogen atoms as isotropic. The coordinates for the hydrogen atoms were generated assuming the standard bond lengths and angles. The space group was $P2_12_12_1$ and the final R value was 6.7%.

Table 1. The crystallographic parameters and experimental conditions

Formula	$C_{18}H_{32}Cl_2N_4NiO_8$
Mw	562.08
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Cell dimension	
a /Å	17.540(2)
b /Å	19.557(2)
c /Å	13.933(2)
U /Å^3	4779(1)
Z	8
D_{obsd} /Mg m^{-3} (temp /K)	1.561 (293)
D_{calcd} /Mg m^{-3}	1.562
F(000)	2352
Abs coeff(μ) /mm^{-1}	1.019
No. of unique reflections (criterion: $\lvert F_o\rvert > 3\sigma(\lvert F_o\rvert)$)	3535
$R=\Sigma(\lvert F_o\rvert-\lvert F_c\rvert)/\Sigma\lvert F_o\rvert$	0.067
$R_w=[\Sigma w(\lvert F_o\rvert-\lvert F_c\rvert)^2/\Sigma w\lvert F_o\rvert^2]^{\frac{1}{2}}$	0.071

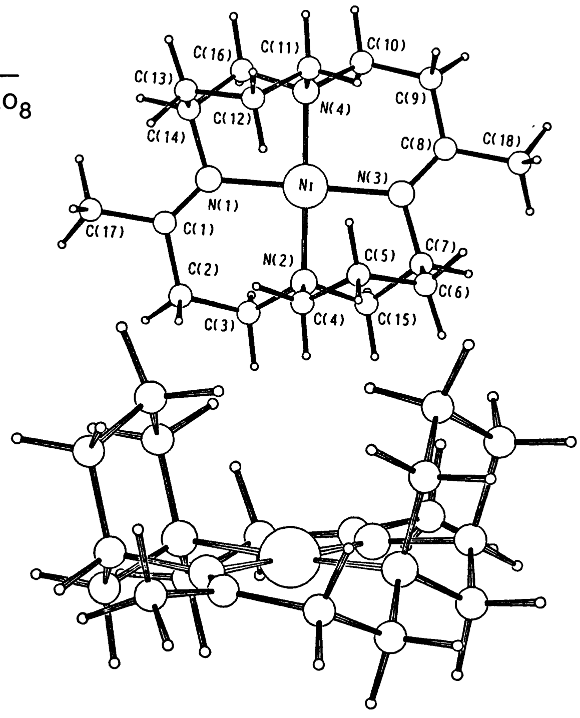
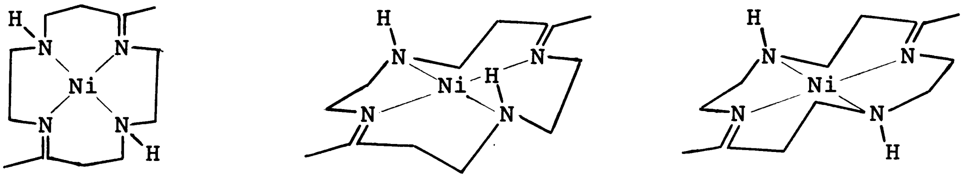


Fig. 1. The molecular structure of the nickel complex of **1**.



(a) (b) (c)

Fig. 2. The diastereomers of the nickel complex (a): (b) N-racemic, (c) N-meso.

Two independent molecules of $[Ni(\mathbf{1})]^{2+}$ are present in the crystal, but no significant difference is observed between them so that the molecular structure of one of them is given in Fig. 1 as the representative. There are also four independent molecules of perchlorate anion, three of which are fixed firmly, and one of which is fixed loosely in the crystal.

There are three rings in the free ligand, i.e. one fourteen-membered and two are six-membered rings. The fourteen membered ring in the diamino-diimine type of complexes are known to take two isomeric structures according to the combination of chiral N-centres, N-rac and N-meso.12,13) In N-rac isomer, the amino protons or their substituents stick out in the same direction, while in N-meso isomer, they stick out in the opposite direction (Fig. 2). In the case of non-substituted complexes, both N-rac and N-meso structures have been obtained.12,13) The figure of the nickel complex of **1** shows that the fourteen-membered ring takes the N-rac form due to the restriction of the piperidine ring of the diamine **3** moiety. The five-membered chelates adopt the λ conformation due also to the restriction of the piperidine ring. The six-membered chelates adopt the δ skew like conformation, distorted due to the presense of C=N double bond. The Ni^{2+} ion is located at the centre of four nitrogen donor atoms, and its deviation from the average plane of four nitrogen atoms is very small (0.036 Å upward and 0.020 Å downward for two independent molecules). Thus the Ni^{2+} ion is trapped firmly inside the macrocycle, and the structure of the complex, as a whole, is quite rigid in its conformation.

The most interesting feature of this complex is the presence of the fences. As can be seen in Fig. 1, this complex has two piperidine rings standing perpendicular to the plane of the four nitrogen donor atoms, looking just like the horns of a hat of the Vikings. Each of two piperidine rings takes a chair conformation, which is the most stable form for aliphatic six-membered ring, and hangs one of its methylenes (C(5),C(12)) over the Ni^{2+} ion, blocking one of the two apical sites. Although the apical site at the other side of the complex is not covered with the fences, the methylenes of six-membered chelates (C(3),C(10)) and five-membered chelates (C(15),C(16)) go out and form chiral environment there.

The crystallographic analysis revealed that the heterocycles in the diamine moieties are effective in fixing the conformation of the macrocycle, and its rigid conformation produces a chiral environment around one of the empty apical sites in the complex. This fact, together with the fact that the N-substitution of diamine does not seriously interfere the macrocycle formation, offers a new opportunity to design and synthesize optically active macrocyclic complexes.

References

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3) I.r. $\tilde{\nu}_{C=N}$=1660 cm^{-1}, $\tilde{\nu}_{Cl-O}$=1100 cm^{-1}. Anal. (**1**)·$2HClO_4$; Found: C,42.71; H,6.91; N,11.06; Cl,14.34%. Calcd for $C_{18}H_{34}Cl_2N_4O_8$: C,42.78; H,6.78; N,11.09; Cl,14.03%.

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8) For $[Ni(\mathbf{1})](ClO_4)_2$: V.s. $\varepsilon(\tilde{\nu}_{max.})$=92 $dm^3mol^{-1}cm^{-1}$ (2.24×10^4 cm^{-1}). C.d. $\Delta\varepsilon(\tilde{\nu}_{ext.})$=+2.9 $dm^3mol^{-1}cm^{-1}$ (2.09×10^4 cm^{-1}), -0.62 $dm^3mol^{-1}cm^{-1}$ (2.39×10^4 cm^{-1}). For $[Cu(\mathbf{1})](ClO_4)_2$: V.s. $\varepsilon(\tilde{\nu}_{max.})$=211 $dm^3mol^{-1}cm^{-1}$ (1.98×10^4 cm^{-1}). C.d. $\Delta\varepsilon(\tilde{\nu}_{ext.})$=+1.31 $dm^3mol^{-1}cm^{-1}$ (2.04×10^4 cm^{-1}) in aqueous solution.

9) ^1H NMR. $\delta(CH_3)$=2.21ppm(s) measured in D_2O after changing the counter anion to the chlorides (ref. DSS).

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