Synthesis and Characterization of 5,5,7,12,12,14-Hexamethyl-1,4,8,11-tetraazacyclotetradecane-N',N'''-diacetic Acid and Its Transition Metal Complexes; Crystal Structure of the Nickel(II) Monohydrogen Bromide Monohydrate Complex of this Macrocycle*

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Abstract

The synthesis and characterization of a new 14-membered tetraazamacrocyclic ligand 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-N',N'''-diacetic acid (H_2L^2) are reported. Cobalt(III), nickel(II) and copper(II) complexes with this ligand were prepared and their IR and visible spectra studied.

The molecular structure of the complex $NiL^2 \cdot HBr \cdot H_2O$ was proved by single-crystal X-ray analysis. The compound crystallizes in the space group $P2_1/n$, with cell parameters $a = 16.7109(13)$, $b = 9.0539(9)$, $c = 17.0277(13)$ Å, $\beta = 107.46(6)°$ and $Z = 4$. The structure was solved by direct and Fourier methods and refined by full matrix least square calculation to $R = 0.042$ for 4355 observed reflections ($I > 3\sigma(I)$). The complex shows a *cis*-octahedral geometry with the macrocycle coordinated in a folded configuration to four sites around the central nickel atom. The two carboxylate groups of the side chain are on the same side of the approximate plane of the macrocycle.

Introduction

There is considerable current interest in the synthetic macrocycles featuring ionizable functional groups and their metal complexes [1–5]. The reasons for this interest may arise from the possibilities of using those macrocycles and complexes as models for systems of biological interest, and from the exceptional thermodynamic and kinetic properties which enable them to be used practically.

Several authors [2–4] have reported that the reactions of certain tetraazamacrocycles with chloroacetic acid in aqueous alkali medium afford the persubstituted products. Kaden and his co-workers [6] have reported a new synthetic routine for the preparation of mono-N-substituted tetraazamacrocycles. Recently a series of the partially alkalated cyclam-(1,4,8,11-tetraazacyclotetradecane) [7] and the partially methylated macrocycle 1,7-dimethyl-1,4,7,10-tetraazacyclododecane [8] have been reported, but the partially N-substituted hexamethyl-tetraazamacrocyclic diacetic acids have not yet been reported.

By the direct reaction of bromoacetic acid with C-meso-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane(L), we have synthesized two partially N-substituted tetraazamacrocycles: 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-N'-acetic acid (HL^1) and 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-N',N'''-diacetic acid (H_2L^2). The stereochemistry of the latter was definitely proved by determining the X-ray structure of its nickel monohydrogen bromide monohydrate complex, $NiL^2 \cdot HBr \cdot H_2O$.
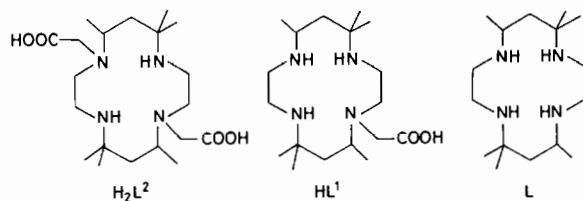
Experimental

All chemicals used were of analytical grade. The ligand L was prepared as described in the literature [9], and characterized by elemental analysis and IR spectroscopy.

Infrared spectra were recorded on a Nicolet 170Sx spectrophotometer. UV-Vis spectra were recorded on a Shimadzu UV-240 spectrophotometer. Conductivity measurements were made with a DDS-11A conductometer. Elemental analyses were performed by the Centre of Structure and Elemental Analysis of China University of Science and Technology.

Preparation $HL^1 \cdot 2HBr \cdot H_2O$ (A)

To 41.7 g (0.3 mol) bromoacetic acid in 150 ml water, 12.0 g (0.3 mol) NaOH in 100 ml cold water was added in such a way that the temperature remained below 5 °C. Then 32.0 g (0.1 mol) L in 250 ml methanol and 31.8 g (0.3 mol) Na_2CO_3 were added. The mixture was stirred and the temperature was maintained at 65 °C for 24 h. The reaction mixture was then cooled and filtered. The filtrate was concentrated to 100 ml and acidified to pH 4.8 with concentrated hydrobromic acid. The solution was placed in a refrigerator overnight. A light cream or white precipitate formed. The filtered product yielded 14 g (26%). Mp (dec) 235–237 °C. *Anal.* Found: C, 41.38; H, 8.06; N, 10.51. Calcd. for $C_{18}H_{42}N_4O_3Br_2$(monohydrate): C, 41.39; H, 8.11; N, 10.72%. IR: 3360, 3400 (OH); 3200 (NH). 2650–2900 (NH_2^+); 1730 (COOH) (KBr discs).

$H_2L^2 \cdot 2HBr \cdot 8H_2O$, (B)

The filtrate in the above preparation was further acidified with hydrobromic acid to pH 3 and then placed in a refrigerator overnight. White crystals formed. The filtrated product yielded 28 g (39%). Mp (dec) 258–260 °C. *Anal.* Found: C, 33.93; H, 8.10; N, 7.89. Calcd. for $C_{20}H_{58}N_4O_{12}Br_2$: C, 34.00; H, 8.28; N, 7.94%. IR: 3400 (OH); 2860 (NH_2^+); 1732 (COOH) (KBr discs).

$NiL^2 \cdot HBr \cdot H_2O$

350 mg B (0.5 mmol) and 327 mg (0.1 mmol) $NiBr_2 \cdot 6H_2O$ were dissolved in 20 ml water, and the pH was successively adjusted to 5 with NaOH. After heating for 2 h, the pH was adjusted to 1 with hydrobromic acid. While the solution was concentrated in a bath, violet crystals precipitated. These were collected and air dried to give 180 mg (64%) products. *Anal.* Found: C, 43.18; H, 7.49; N, 9.93. Calcd. for $NiC_{20}H_{41}N_4O_5Br$ (monohydrate): C, 43.19; H, 7.43; N, 10.07%.

$CoL^2Br \cdot 4H_2O$

350 mg B (0.5 mmol) and 326 mg (1 mmol) $CoBr_2 \cdot 6H_2O$ were dissolved in 20 ml water, the pH was successively adjusted to 5 with NaOH. After heating for several hours the solution turned intense red and needle crystals were obtained upon standing. These were collected and air dried to give 220 mg (72%) products. *Anal.* Found: C, 39.57; H, 7.49; N, 9.32. Calcd. for $CoC_{20}H_{46}N_4O_8Br$-(tetrahydrate): C, 39.42; H, 7.61; N, 9.19; Co, 9.67%.

$CuL^2 \cdot HBr \cdot 10H_2O$

350 mg B (0.5 mmol) and 166 mg (0.5 mmol) $CuBr_2 \cdot 6H_2O$ were dissolved in 20 ml water, the pH was adjusted to 1 with hydrobromic acid. After heating for several hours at 80 °C, light blue cubic crystals were obtained upon standing at room temperature. These were collected and air dried to give 210 mg (58%) products. *Anal.* Found: C, 33.41; H, 8.29; N, 7.70; Cu, 8.51. Calcd. for $CuC_{20}H_{59}N_4O_{14}Br$(decahydrate): C, 33.22; H, 8.22; N, 7.74; Cu, 8.79%.

$CuL^2 \cdot HNO_3 \cdot 2H_2O$

350 mg B (0.5 mmol) was dissolved in 20 ml water, the Br^- ions were removed with the strong basic ion exchange resin 201 × 4. Then 159 mg (0.5 mmol) $Cu(NO_3)_2 \cdot 6H_2O$ was added to the solution, the pH was successively adjusted to 5 with NaOH. After heating for several hours in a bath, blue crystals were obtained upon standing. These were collected and air dried to give 160 mg (57%) products. *Anal.* Found: C, 42.71; H, 8.08; N, 12.45; Cu, 11.10. Calcd. for $CuC_{20}H_{43}N_5O_6$(dihydrate): C, 42.81; H, 7.73; N, 12.50; Cu, 11.28%. IR: 1384 (NO_3^-) (KBr discs).

$Cu_2L^2Br_2$

350 mg B (0.5 mmol) and 398 mg (1.2 mmol) $CuBr_2 \cdot 6H_2O$ were dissolved in 10 ml water, the pH was adjusted to 5 with NaOH. After heating for several hours in a bath, deep green crystals precipitated. These were collected and air dried to give 140 mg (40%) products. *Anal.* Found: C, 35.24; H, 5.74; N, 8.83; Cu, 18.82. Calcd. for $Cu_2C_{20}H_{38}N_4O_4Br_2$: C, 35.05; H, 5.59; N, 8.17; Cu, 18.54%.

Crystallographic Study

Violet crystals suitable for X-ray determination were obtained under a controlled rate of evaporation of the aqueous solution of $NiL^2 \cdot HBr \cdot H_2O$ in a 80 °C bath for one or two days.

The crystal data $C_{20}H_{38}N_4O_4Ni \cdot HBr \cdot H_2O$, $M_r = 556.17$, space group $P2_1/n$, $a = 16.7109(13)$, $b = 9.0539(9)$, $c = 17.0277(13)$, $\beta = 107.46(6)°$, $Z = 4$, $D_c = 1.498$ g cm^{-3}.

The intensity data was collected on an Enraf-Nonius CAD-4 automatic diffractometer, where 4762 reflections were measured. LP correction was applied to the data but no correction for absorption was made. The structure was solved by direct method and standard Fourier synthesis and positional and thermal parameters of all non-hydrogen atoms were refined by a full matrix least-squares method to R = 0.042 for 4355 observed reflections with $I > 3\sigma(I)$.

TABLE I. Final Positional Parameters ($\times 10^4$) for Non-hydrogen Atoms of $NiL^2 \cdot HBr \cdot H_2O$ with e.s.d.s in Parentheses

Atom	x	y	z
Br	−3061.1(3)	4821.8(6)	1866.1(3)
Ni	4719.8(3)	3719.5(6)	2710.3(3)
O1	3898(2)	1949(3)	2527(2)
O2	3898(2)	4402(3)	3440(2)
O3	3792(2)	−292(3)	3012(2)
O4	2519(2)	4451(4)	3161(2)
O5	3333(3)	1563(5)	−1417(3)
N1	3916(2)	5173(4)	1920(2)
N4	5588(2)	5473(4)	2961(2)
N8	5496(2)	2353(4)	3590(2)
N11	5198(2)	2672(4)	1853(2)
C2	4237(3)	6661(5)	2230(3)
C3	5181(3)	6732(5)	2426(3)
C5	6053(3)	5864(5)	3853(3)
C6	6458(3)	4461(6)	4296(3)
C7	5920(3)	3147(6)	4386(3)
C9	6102(3)	1754(5)	3175(3)
C10	5653(3)	1358(5)	2286(3)
C12	4625(3)	2381(5)	976(3)
C13	3816(3)	3325(6)	810(3)
C14	3893(3)	4957(5)	1040(3)
C15	3086(3)	4956(5)	2056(3)
C16	3199(3)	4584(5)	2950(3)
C17	4950(3)	1170(5)	3739(3)
C18	4153(2)	935(4)	3027(3)
C19	5458(3)	6565(6)	4274(3)
C20	6761(3)	6965(6)	3875(4)
C21	6453(3)	2111(7)	5049(3)
C22	4348(3)	782(6)	833(3)
C23	5109(3)	2798(6)	373(3)
C24	3209(3)	5879(6)	443(3)

The maximum residual peak on final difference Fourier map was 0.7 e/$Å^3$. The final atomic coordinates are listed in Table I.

Results and Discussion

The synthesis of partially N-substituted hexamethyl-tetraazamacrocycles by alkylation of L with bromoacetic acid was straightforward. No persubstituted product was formed. This phenomenon was probably due to the steric hindrance caused by the increasing number of methyl substituents in the neighborhood of the unsubstituted amine groups. The difunctionalized ligand H_2L^2, in principle, occurs in several configurations arising from chiral -substituted nitrogen centers presented [10]. In addition the isomers originate from the position of the hydrogens of the NH system (Fig. 1).

Because two tertiary nitrogen donors are present in ligand H_2L^2, their relative stereochemistry is fixed so long as they remain coordinated to the metal since
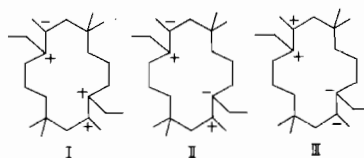

Fig. 1. Configuration of ligand H_2L^2. The + indicates that the substituted group is above the plane of the flattened macrocycle. The − indicates that it is below.

the conjugate base pathway for inversion is no longer available. We found that the nickel complex of this ligand has stereochemistry I. It forms the *cis*-NiN_4O_2 structure in which the parent cyclic tetraamine is folded. The existence of another two stereoisomers is possible. They will form the *trans*-enclosed six coordinated metal complexes.

Metal Complexes of Ligand H_2L^2

Ligand H_2L^2 has six potential coordinating atoms. The metal complexes were studied in part in solution, but mainly by preparing several crystalline compounds. According to the elemental analysis, this ligand forms complexes with Co(III), Ni(II) and Cu(II) by a metal to ligand ratio of 1:1. With Cu(II), there exists another complex with a ratio of 2:1, which is insoluble in most solvents even in DSMO.

All the information from the IR, UV-Vis spectra concerning the species ML^2 seems to infer that the metal ions are in the pseudooctahedral environment coordinated to four nitrogen and two oxygen atoms.

The strong band in the IR spectrum of $CuL^2 \cdot HNO_3 \cdot 2H_2O$ at 1384 cm^{-1} indicates that the NO_3^- group plays a role of uncoordinated free ion instead of a bidentate or unidentate. By means of argentimetry, it is showed that the Br$^-$ ion is in the outsphere of the 1:1 metal complex species. All the solutions of 1:1 Cu(II) and Ni(II) complex species give acidic reactions, and the neutralization titration of them shows that there is a free H$^+$ ion in each molecule of the complex. Therefore, it is possible that HNO_3 or HBr is present in these complex as an 'acid molecule of crystallization'.

The 2:1 Cu(II) complex was obtained when two or more equivalents of copper ion were added to the ligand. Its IR spectrum exhibits bands at 3180 (NH) and 1580 (COO$^-$), its visible reflectance spectrum has one asymetrical band at 608 nm. A suggestion for the coordination sites and geometry of this complex is more difficult for the 1:1 complex. It is possible that this compound could be polymeric.

The Structure of $NiL^2 \cdot HBr \cdot H_2O$

The crystal consists of monomeric complex molecule of the formula indicated and a molecule of hydrogen bromide and a molecule of water. The overall structure of the macrocyclic is shown in the
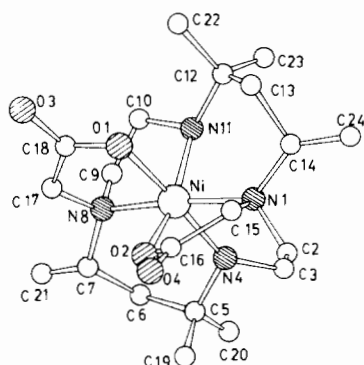
Fig. 2. Structure of the octahedral nickel(II) complex with 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-N',N'''-diacetic acid (H_2L^2) in $NiL^2 \cdot HBr \cdot H_2O$.
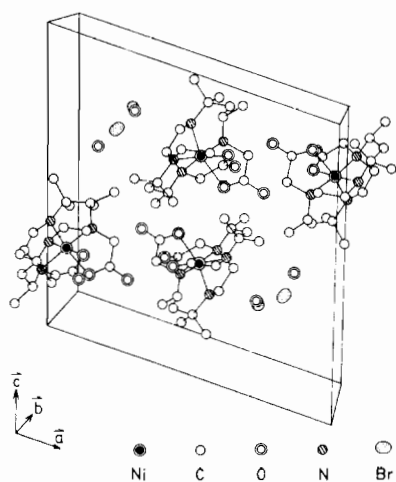

Fig. 3. ORTEP stereoview of the unit cell of $NiL^2 \cdot HBr \cdot H_2O$.

TABLE II. Selected Interatomic Distances (A) and Angles (deg) in $NiL^2 \cdot HBr \cdot H_2O$

Distances

Ni–N1	2.073(3)	C3–N4	1.492(5)
Ni–O2	2.199(5)	N4–C5	1.521(5)
Ni–O3	2.065(3)	C5–C6	1.528(6)
Ni–N4	2.107(3)	C6–C7	1.526(6)
Ni–N8	2.072(3)	C7–N8	1.510(5)
Ni–N11	2.091(3)	N8–C9	1.498(5)
O1–C18	1.238(5)	N8–C17	1.478(5)
O2–C16	1.228(5)	C9–C10	1.518(6)
O3–C18	1.261(4)	C10–N11	1.483(5)
O4–C16	1.296(5)	N11–C12	1.535(5)
N1–C2	1.487(5)	C12–C13	1.551(6)
N1–C14	1.500(5)	C13–C14	1.524(6)
N1–C15	1.487(5)	C15–C16	1.513(6)
C2–C3	1.513(6)	C17–C18	1.523(6)

Angles

O1–Ni–O2	78.74(11)	Ni–N4–C3	106.91(24)
O1–Ni–N1	97.03(11)	Ni–N4–C5	119.61(24)
O1–Ni–N4	176.78(12)	C3–N4–C5	115.84(32)
O1–Ni–N8	83.70(11)	N4–C5–C6	108.41(33)
O1–Ni–N11	85.33(11)	C5–C6–C7	120.71(34)
O2–Ni–N1	78.18(11)	Ni–N8–C7	112.82(24)
O2–Ni–N4	100.41(12)	Ni–N8–C9	103.91(23)
O2–Ni–N8	96.94(11)	Ni–N8–C19	105.78(22)
O2–Ni–N11	163.06(11)	C7–N8–C9	113.25(29)
N1–Ni–N4	85.80(13)	C7–N8–C17	109.74(30)
N1–Ni–N8	174.79(12)	C9–N8–C17	111.00(31)
N1–Ni–N11	98.30(12)	N8–C9–C10	110.77(31)
N4–Ni–N8	93.35(12)	C9–C10–N11	109.40(32)
N4–Ni–N11	95.81(12)	Ni–N11–C10	105.26(24)
N8–Ni–N11	86.90(12)	Ni–N11–C12	119.95(22)
Ni–O1–C18	113.18(24)	C10–N11–C12	115.01(31)
Ni–O2–C16	106.36(25)	N11–C12–C13	109.75(31)
Ni–N1–C2	104.50(23)	C12–C13–C14	119.04(35)
Ni–N1–C14	112.58(24)	N1–C14–C13	111.01(34)
Ni–N1–C15	105.57(23)	N1–C15–C16	110.25(33)
C2–N1–C14	111.82(32)	O2–C16–C15	121.35(37)
C2–N1–C15	108.59(32)	N8–C17–C18	113.67(33)
C14–N1–C15	113.22(32)	O1–C18–C17	118.88(36)
N1–C2–C3	111.00(32)	C6–C7–N8	114.34(33)
C2–C3–N4	110.86(32)		

drawing of the molecule (Fig. 2). The ORTEP stereoview of the unit cell of $NiL^2 \cdot HBr \cdot H_2O$ appears in Fig. 3. A list of selected bond distances and angles is given in Table II.

The nickel atom in the complex is six coordinated to the four nitrogen atoms in the macrocycle and two oxygen atoms of the appended carboxylate groups. As shown in Fig. 2, this is achieved by the folding macrocycle along the N1–Ni–N8 diagonal, which allows both of the carboxylic oxygen atoms to coordinate in a cis-arrangement. Probably, this cis-NiN_4O_2 structure is attributed to the stereochemical pattern of the ligand.

The Ni–N4 and Ni–N11 (secondary) distances are 2.107 and 2.091 Å respectively. The values are typical for the octahedral triplet ground state Ni(II) coordinated to secondary amine group.

In a partially methylated macrocycle 1,7-dimethyl-1,4,7,10-tetraazacyclododecane, the Ni–N(secondary) distances (2.051 and 2.072 Å) are shorter than that of Ni–N(tertiary) (2.153 and 2.160 Å). However, in $NiL^2 \cdot HBr \cdot H_2O$, the distances of Ni–N(secondary) (2.091 and 2.107 Å) are longer than that of Ni–N(tertiary) (2.072 and 2.073 Å). The fact is probably due to the electron-attracting inductive effect of the appended carboxylate groups.

There is no hydrogen-bond between the two non-coordinated carboxyl oxygen atoms and water molecules. The latter is near the Br⁻ with interatomic distances of 3.361 and 3.385 Å respectively.

Acknowledgements

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