Copper(II) and Nickel(II) Complexes of *N*,*N*-Bis(2-hydroxyethyl)octamethyl-1,4,8,11-tetraazacyclotetradecane

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Reaction of ethylene oxide with the 1,4,8,11-tetraazacyclotetradecanes Me_8[14]ane L_B (diaxial-diequatorial with respect to the methyl substituents at the secondary ring carbons) and L_C (axial-triequatorial) yielded the N4,N11-disubstituted 2-hydroxyethyl (Y) derivatives L_{BY} (diaxial-diequatorial) and L_{AY} (all-equatorial). These new ligands interact with $Cu(ClO_4)_2$ to produce octahedral blue-violet $[CuL_{BY}][ClO_4]_2$ and deep-blue $[CuL_{AY}][ClO_4]_2$, with the hydroxyl groups of the $–CH_2–CH_2–OH$ arms in axial positions. Reaction of L_{BY} with nickel(II) acetate and subsequent addition of $Li(ClO_4)$ yielded square-planar yellow $[NiL_{BY}][ClO_4]_2$. Characterisation has been carried out on the basis of analytical, spectroscopic, conductometric and magneto-chemical data. The structures of L_{BY} and $[CuL_{AY}][ClO_4]_2$ have been confirmed by X-ray diffraction analyses. The antifungal and antibacterial activities of these compounds have been studied against some phytopathogenic fungi and bacteria.

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Introduction

Biogenic macrocyclic tetraaza ligands employed in metal-ion complexation such as in heme proteins, chlorophyll, vitamin B_{12}, or the factor F_{430} of methyl-coenzyme-M reductase in methanogenesis are structurally complex systems which, generally and perhaps simplistically, may be considered rigid planar cyclic structures carrying pendent functional groups acting as functional components at the coordination sites.[1,2] The design and synthesis of macrocyclic systems carrying such functional groups, mimicking the properties of their natural counterparts, is thus a multifarious problem.

In order to synthesise the requisite type of super-structured macrocycles, the obvious approach is to first prepare the more basic macrocyclic ligand, and then attach suitable pendent hydrocarbon chains to the periphery. Thus, a number of macrocycles carrying N-substituents have been prepared by alkylation reactions,[3] starting from the basic isomeric octamethyltetraazacyclotetradecanes Me_8[14]anes L_A, L_B and L_C, where the indexes A, B and C denote the differing stereochemistries with respect to the methyl substituents attached to the chiral carbons of the [14]ane in its chair conformation. Thus, A represents all-equatorial, B diaxial-diequatorial and C axial-triequatorial orientations.[4,5] To approach the biogenic ligands, attempts have been made to attach pendent functional groups to the N donors and consequently to influence the ligating ability of the original N-donor ligands. Thus, in the reactions of L_B with acrylonitrile, two of the NH protons have been substituted by $- CH_2CH_2CN$.[6] This bis(2-cyanoethyl) derivative of L_B has been designated L_{BX}, and the dimethyl derivatives of L_B and L_C, prepared by methylation with methyl iodide,[7] have been denoted L_{BZ} and L_{CZ}. The structures of L_{BX} [6] and L_{BZ} [7] have been confirmed by X-ray crystallography. In the present contribution, we report on the synthesis and coordination behaviour towards Cu^{II} and Ni^{II} of the reaction products obtained by reacting L_B and L_C with ethylene oxide, yielding the bis(2-hydroxyethyl)-substituted ligands L_{BY} and L_{AY} where, in the case of the formation of L_{AY}, a conformational change took place.

Results and Discussion

Ligands L_{BY} and L_{AY}

Passage of ethylene oxide through aqueous suspensions of L_B and L_C, and subsequent extraction with chloroform, evaporation of the $CHCl_3$ extracts and re-crystallisation from $CH_3OH/CHCl_3$ (L_{BY}) or CH_3OH/Et_2O (L_{AY}) yielded the ligands in the form of white products (Scheme 1). The melting points of L_{BY} (175 °C) and L_{AY} (160 °C) clearly differ from those of the parent ligands L_B (122 °C) and L_C (85 °C). Formation of the bis- rather than the tetrakis(2-hydroxyethyl) derivatives observed in case of the analogous cyclam-type macrocycles[8] can be attributed to steric effects

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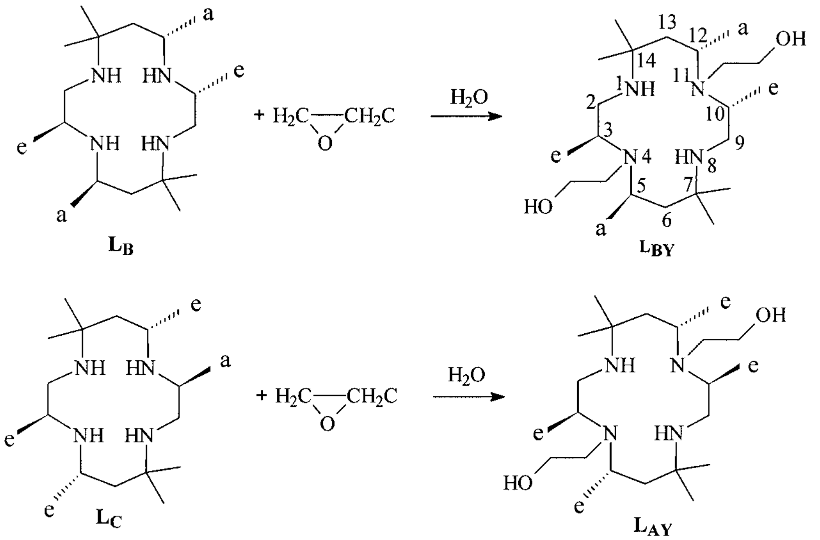


Scheme 1

created by the eight peripheral methyl groups. The fragmentation patterns obtained from the mass spectra of L_{BY} and L_{AY} (vide infra) clearly indicate that substitution of N−H protons by $-CH_2CH_2-OH$ groups has taken place at N4 and N11 only. This substitution was confirmed by the X-ray structure of L_{BY} and the copper(II) complex of L_{AY}. X-ray and ^1H NMR analyses (vide infra) of L_{BY} and L_{AY} reveal that the diaxial-diequatorial arrangement for L_{BY} is retained, while the configuration has changed to all-equatorial in the case of L_{AY}.

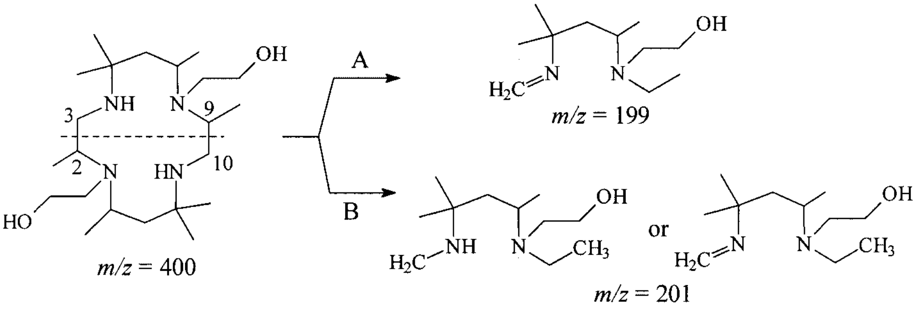
The infrared spectra (Table 1) show the ν_{N-H}, ν_{C-H}, ν_{C-C} and ν_{CH_3} stretching bands in the expected region. A band at 3740 cm^{-1} for L_{BY}, and 3500 cm^{-1} for L_{AY}, indicates the presence of the OH group in these compounds, as do the ν_{C-OH} bands at 1260 and 1060 cm^{-1}; the primary alcoholic hydroxyl group usually shows strong ν_{CO} stretching bands at 1350 to 1260, and 1050 cm^{-1}.

Table 1. Selected IR data (cm^{-1})

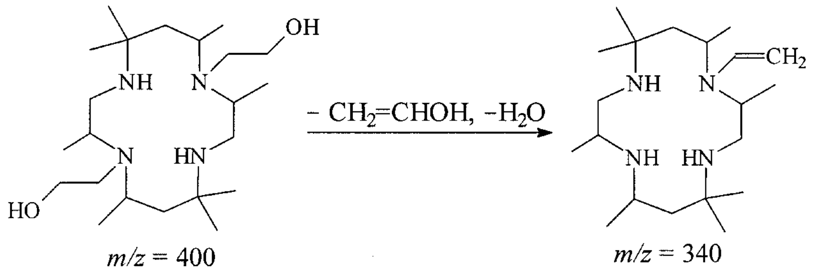
	ν_{N-H}	ν_{C-H}	ν_{CH_3}	ν_{C-C}	ν_{M-N}	ν_{ClO_4}	ν_{OH}
L_{BY}	3110	2990	1360	1160	–	–	3740
L_{AY}	3250	2970	1380	1135	–	–	3500
$[NiL_{BY}][ClO_4]_2$	3100	2985	1390	1180	540	1110, 625	3720
$[CuL_{BY}][ClO_4]_2$	3200	2990	1390	1175	570	1140, 625	3500
$[CuL_{AY}][ClO_4]_2$	3190	2995	1380	1175	525	1100, 620	3400

The mass spectrum of L_{BY} exhibits the molecular-ion peak at $m/z = 400$, while that of L_{AY} is at $m/z = 403$, corresponding to $[M + 3]^+$. Both the isomeric ligands show more or less the same fragmentation pattern, although the intensities of the peaks differ. The basic peaks are at $m/z = 199$ for L_{BY} and 171 for L_{AY}. This difference may reflect the stereochemical differences. The prominent fragmentations are presented in Schemes 2−5. The basic peak at $m/z = 199$ for L_{BY} comes about by the concomitant cleavage of the C2−C3 and C9−C10 bonds (α-cleavage),[4,9,10] followed by the loss of one H atom (path A in Scheme 2). The second intense peak at $m/z = 201$ also arises from this cleavage with capture of an H atom (path B). The molecular ion can also undergo fragmentation by C−N bond rupture of one of the N-pendent groups with elimination of vinyl alcohol, followed by hydrogen rearrangement and elimination of an H_2O molecule from the other 2-hydroxyethyl group, providing an ion at $m/z = 340$ (Scheme 3).

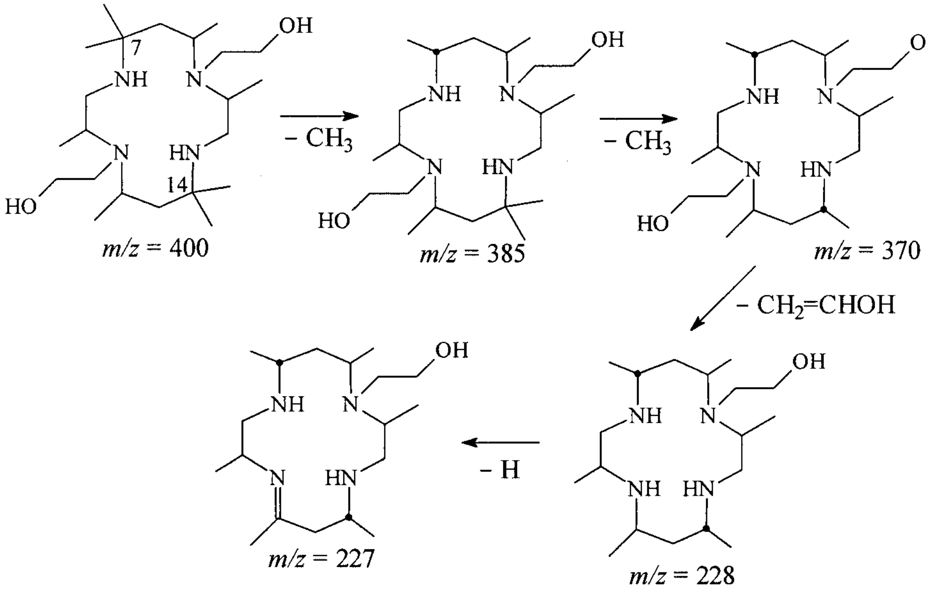
Additionally, the molecular ion can successively lose two methyl radicals from the more crowded α-carbons C7 and C14 to form ions at $m/z = 370$, from which removal of vinyl alcohol by C−N bond rupture in one of the N-pendent groups, followed by rearrangement of H atoms and finally



Scheme 2



Scheme 3

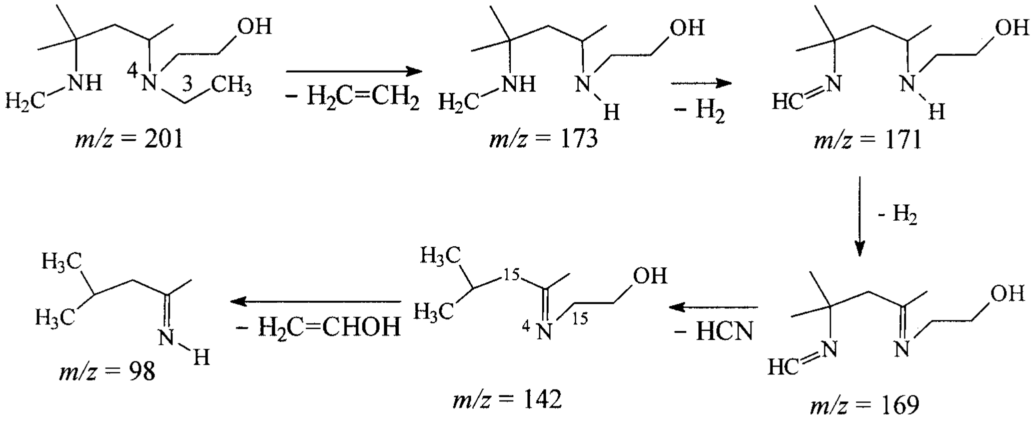


Scheme 4

elimination of H_2, results in an ion at $m/z = 227$ (Scheme 4).

Alternatively, the basic peak at $m/z = 171$ for L_{AY} (Scheme 5) may arise from the $m/z = 201$ fragment by C3−N4 bond rupture with elimination of ethylene, followed by rearrangement and successive removal of H_2. The resulting fragment at $m/z = 171$ can further lose a hydrogen molecule to provide the peak at $m/z = 169$. This fragment, on removal of hydrogen cyanide, yields an ion at $m/z = 142$ which, by C15−N4 bond cleavage and elimination of vinyl alcohol, can produce the ion at $m/z = 98$.

The ^1H NMR spectrum of ligand L_{BY} (Table 2) shows two singlets at $\delta = 1.108$ and 1.147 ppm corresponding to six protons each that can be assigned to the geminal bis(methyl) groups. In addition, there are two doublets at $\delta = 0.982$ and 0.879 ppm, each corresponding to six protons. This requires that C3,C10 and C5,C12 should be in pairwise equivalent configurations. The upfield doublet can be



Scheme 5

Table 2. ^{1}H NMR spectroscopic data of the ligands[a]

Ligands	Geminal dimethyl	Methyl on chiral carbon atoms	CH_2, CH and NH	OH
L_{BY}	1.108 s (*e*, 6 H) 1.147 s (*a*, 6 H)	0.982 d (*a*, 6 H) 0.879 d (*e*, 6 H)	2.047 m 2.353 m 3.168 m 3.408 m	not resolved
L_{AY}	1.082 s (*e*, 6 H) 1.369 s (*a*, 6 H)	1.145 d (*e*, 6 H) 1.199 d (*e*, 6 H)	2.20−2.45 m 3.10−3.35 m	2.897 br

[a] s = singlet, d = doublet, *a* = axial, *e* = equatorial, br = broad, m = multiplet.

assigned to the equatorial and the downfield doublet to the axial methyls. Thus, a diaxial-diequatorial arrangement has been assigned to L_{BY}, in analogy to its parent ligand L_B, an assignment which is confirmed by its X-ray structure. The presence of a hydroxyl group in L_{BY}, confirmed by IR spectroscopy, is not reflected by any clear singlet for OH protons in the ^{1}H NMR spectroscopy. This may be due to rapid intermolecular chemical exchange of the hydroxyl protons. The α- and β-methylene, methine and NH protons appear as poorly resolved multiplets at δ = 2.047, 2.353, 3.168 and 3.408 ppm, respectively.

The geminal bis(methyl) groups of L_{AY} are represented by two singlets at δ = 1.082 (equatorial) and 1.369 ppm (axial). Two doublets at δ = 1.145 and 1.199 ppm, each representing six protons, correspond to the methyl groups C3, C5, C10 and C12 in the equatorial positions. This all-equatorial arrangement was also confirmed by the X-ray structure of $[CuL_{AY}][ClO_4]_2$ (see below). A sharp singlet at δ = 2.897 ppm in the ^{1}H NMR spectrum of ligand L_{AY} can be assigned to the OH protons. The signals due to methylene, methine and N−H protons overlap and could not be resolved clearly.

Representations of the molecular structure of L_{BY}, including the numbering scheme, and the unit cell are shown in Figure 1, the caption of which also contains selected bonding parameters. The molecules are pairwise related to each other by an inversion centre. The cyclic [14]ane skeleton is in the chair conformation, with the methyl groups on the secondary ring carbons (C5, C9, C16, C20) alternately in the axial and the equatorial positions. The angles between the normals of the mean planes constituting the two chairs are as follows (cf. also Figure 1, bottom): molecule 1: C5,C11,C2A,N1A,C4A,C11A,C3,N1,C4 (plane 1)/C5,N2,C9,C11 = 92.6°; (plane 1)/C5A,N2A,C9A,C11A =

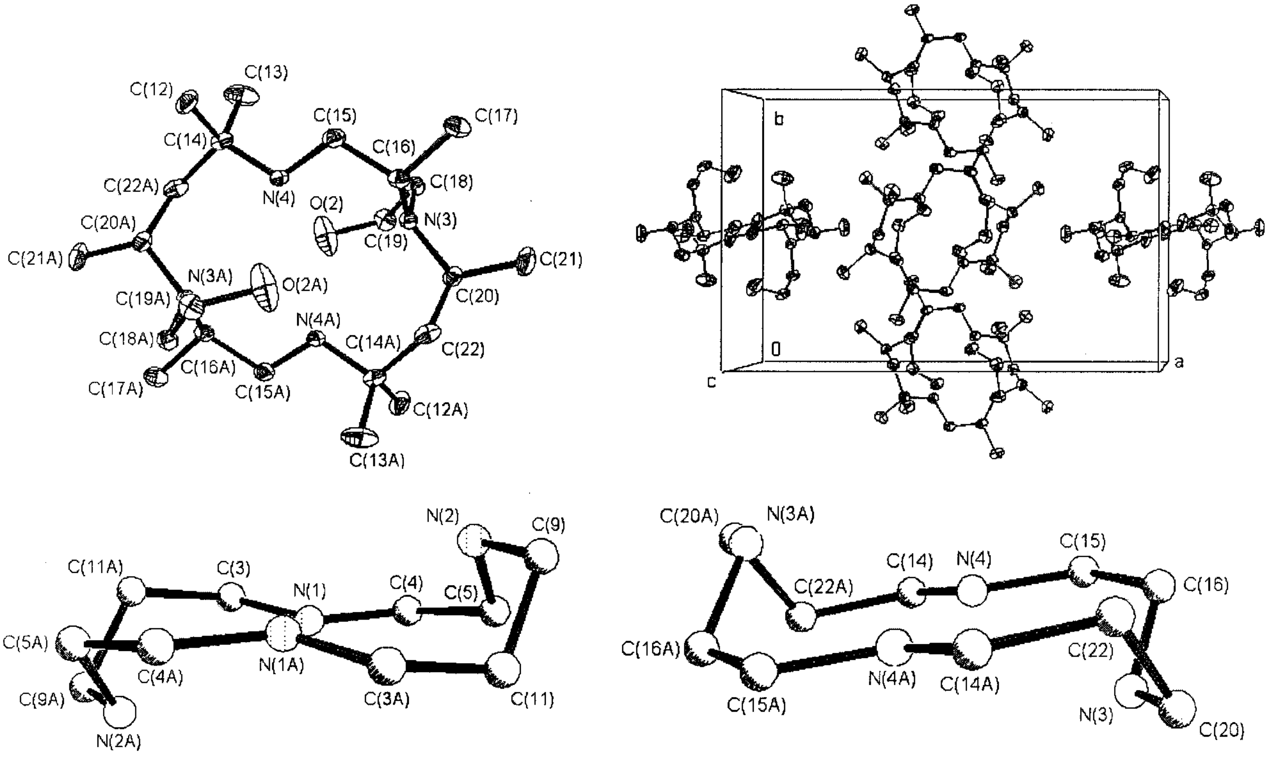


Figure 1. ORTEP presentation of the molecular structure (top left), cell drawing (top right) and the [14]ane skeletons (bottom) of L_{BY}; selected bond lengths (Å) and angles (°): N1−C4 1.464(2), N1−C3 1.484(2), N2−C5 1.4709(19), N2−C9 1.473(2), N2−C7 1.4591(19), C7−C8 1.528(2), C8−O1 1.409(2); C3−N1−C4 115.60(12), C5−N2−C9 117.87(12), C7−N2−C9 113.06(12), C7−N2−C5 115.66(12), N2−C7−C8 111.74(12), C7−C8−O1 112.88(13)

72.3°; molecule 2: C16,C22,C14A,N4A,C15A,C16A,C22A,C14,N4,C15 (plane 2)/C16,N3,C20,C22 = 87.7°; (plane 2)/C16A,N3A,C20A,C22A = 106.6°. The pendent ethanol substituents on N2 and N3 are oriented axially, with the OH groups bent towards the cavity spanned by the four nitrogens. Only one of the OH groups, O1, is involved in an intramolecular hydrogen bonding interaction [*d*(OH···N2) = 2.839Å].

Complexes $[Ni(L_{BY})][ClO_4]_2$ and $[CuL][ClO_4]_2$ ($L = L_{BY}$ or L_{AY})

The reaction of nickel(II) acetate tetrahydrate with L_{BY} and subsequent addition of lithium perchlorate in methanolic solution yielded yellow, square-planar $[Ni(L_{BY})][ClO_4]_2$. The formulation is assigned on the basis of analytical data, conductance and magneto-chemical measurements, and IR- and UV-spectral analyses. The IR spectrum (Table 1) of the complex shows a ν_{N-H} band at around 3200 cm^{-1}, and the perchlorate bands around 1100 cm^{-1} and 620 cm^{-1}. A band at 3720 cm^{-1} demonstrates the presence of the pendent OH group. The molar conductivity value of 173 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$ (Table 3) in acetonitrile correspond to a 1:2 electrolyte — the two ClO_4^- anions are outside the coordination sphere. Similar results were found in aqueous solution (Table 3). The magneto-chemical measurement of $[Ni(L_{BY})][ClO_4]_2$ is in good agreement with square-planar diamagnetic nickel(II). The stereochemical assignment was based on ^1H NMR spectroscopy.

The electronic absorption spectrum of $[Ni(L_{BY})][ClO_4]_2$ displays a *d-d* band at 474 nm, which can be assigned to the $^1A_1g \rightarrow {}^1B_1g$ transition. The results of our complexes fit well with those for Ni^{II} complexes of other saturated aza macrocycles.[11] The relatively high ε_{max} value of 82 $dm^3\cdot mol^{-1}\cdot cm^{-1}$ indicates that the axial positions are free. Octahedral Ni^{II} complexes have low extinction coefficients in the range of 20−30 $dm^3\cdot mol^{-1}\cdot cm^{-1}$. The pendent hydroxy groups of L_{BY} in principle do have coordinating properties. The experimental evidence — the yellow colour, the comparatively high ε for the transition in the visible, and the lack of a shift of the IR band corresponding to OH —, however, shows that this group does not coordinate in the present case. The absorption band at 237 nm in the UV region is assigned to a charge-transfer transition. This band does not provide any information related to the geometry of these complexes. On complexation, the "up" and "down" positions of methyls on chiral carbons in the ligand are retained — no configurational change in the ligand system is to be expected as L_{BY} coordinates.[11,12] The proposed structure of $[Ni(L_{BY})][ClO_4]_2$ is shown in Scheme 6.

Interaction of copper(II) perchlorate hexahydrate with the ligands L_{BY} or L_{AY} in methanolic solution yields the blue-violet to deep-blue complexes $[CuL][ClO_4]_2$. The infrared spectra (Table 1) show ν_{N-H} bands around 3200 cm^{-1} and the perchlorate bands at 1100 and 620 cm^{-1}, as well as the ν_{C-H}, ν_{C-C}, ν_{CH_3} and ν_{Cu-N} bands in the expected positions. For $[CuL][ClO_4]_2$, a strong band at 3500 ($L = L_{BY}$) and a broad band at 3400 cm^{-1} ($L = L_{AY}$) are found, corresponding to OH. The low-frequency shift of these bands with respect to the free ligands indicates coordination of OH to the copper(II) ion, forming octahedral complexes, a coordination mode which was confirmed by the X-ray structure analysis of $[Cu(L_{AY})][ClO_4]_2$.

The molar conductivity of 168−170 in aqueous solution and 148−165 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$ in acetonitrile corresponds to 1:2 electrolytes — an ionic situation. The colour change (from blue-violet and deep-blue to pink) as these complexes are dissolved in water indicates the formation of new complexes in water. The most obvious explanation is the replacement of the hydroxy ligands by water — the formation of diaqua complexes $[CuL(H_2O)_2]^{2+}$ — as in the Cu^{II} complexes with the parent ligands L_B and L_C.[13] On the other hand, solutions of $[Cu(L_{BY})][ClO_4]_2$ and $[Cu(L_{AY})][ClO_4]_2$ in chloroform do not show any conductance, suggesting that the ClO_4^- ions have entered into the coordination sphere to form octahedral bis(perchlorato) complexes $[CuL(ClO_4)_2]$.

The complexes $[CuL][ClO_4]_2$ show broad *d-d* bands at 507−564 nm in acetonitrile, as do other Cu^{II} complexes with tetraza macrocycles.[14,15] Bands around 300 nm can be attributed to copper-ligand charge-transfer transitions. The magnetic moments of 1.68−1.83 μ_B are in good agreement with "normal" copper(II) complexes having one unpaired electron. As the ^1H NMR spectra could not be measured for these paramagnetic complexes, the exact stereochemistry (i.e. axial and equatorial positions of methyls on chiral carbons) could not be determined by NMR spectroscopy. As in the case of the nickel complex (vide supra), and based on the structural determination of the Cu^{II} complex with

Table 3. Selected physico-chemical properties of the complexes[a]

	$[Ni(L_{BY})][ClO_4]_2$	$[Cu(L_{BY})][ClO_4]_2$	$[Cu(L_{AY})][ClO_4]_2$
Solid state	pale yellow	blue-violet	deep blue
μ_{eff} (μ_B)	diamagnetic	1.83	1.68
In MeCN	yellow	pink-violet	blue
λ_{max} (nm) (ε)	474 (82)	507 (194), 303	564 (200), 301
Λ ($\Omega^{-1}\cdot cm^2\cdot mol^{-1}$)	173	165	148
In H_2O	yellow	pink	pink
Λ ($\Omega^{-1}\cdot cm^2\cdot mol^{-1}$)	165	170	168
In $CHCl_3$	−	blue-violet	deep blue
Λ ($\Omega^{-1}\cdot cm^2\cdot mol^{-1}$)	−	none	none

[a] μ = Magnetic moment at 298 K, λ = wavelength in the UV/Vis spectrum, ε = extinction coefficient, Λ = conductivity.

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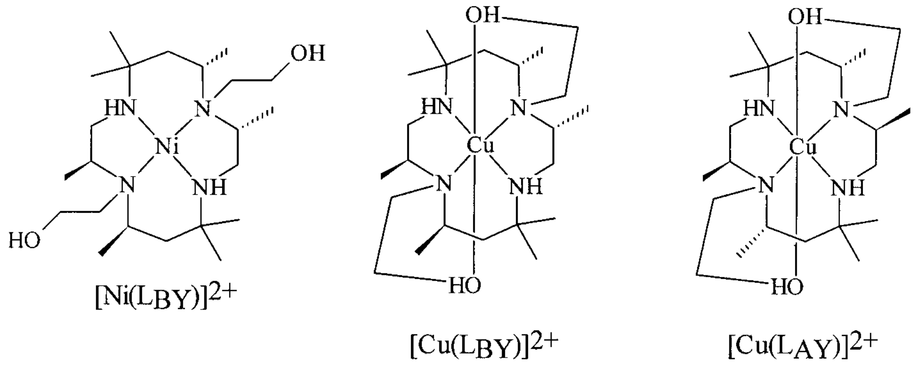

Scheme 6

L_{AY}, configurational changes on complexation are not expected. For structural formulae of the two copper complexes see Scheme 6.

An ORTEP drawing of the molecular structure of the cation $[Cu(L_{AY})]^{2+}$ is represented in Figure 2, showing the distorted octahedral coordination geometry for the copper ion. For selected bonding parameters see the caption to Figure 2. Cu lies on a crystallographic inversion centre. The two ring carbons C6 and C7, and the methyl group C9 (attached to C6), are disordered over two equally populated positions. Together with the four nitrogen donors, the copper ion forms an ideal plane. The deviations of the ring carbons from this plane are as follows (in Å): C3 −0.648, C4 −0.029, C6 −0.47, C6# −1.045, C7 −1.517, C7# −0.606, C8 −0.921. The OH functions are above and below this plane. The O1−Cu−O1A axis is not exactly perpendicular to this plane, but inclined towards the axis N1−Cu−N1A by 13.7°, and towards the axis N2−Cu−N2A by 4.3° (average angle between the normal of the plane and the O1−Cu−O1A axis: 95.6°). The Cu−O distances [2.432(3) Å] are rather long, indicating relatively weak coordination and thus the above-mentioned possibility of the replacement of the two axial positions by water or perchlorate. These OH functions are additionally hydrogen-bonded to the axially oriented perchlorate anions [$d(ClO_4^-{\cdots}OH)$ = 2.797 and 3.206 Å]. The angles at the carbons of the 2-hydroxyethyl arm of coordinated L_{AY} deviate somewhat from those of the free ligand L_{BY} (116.5° at C1 vs. 111.5°; 108.6° at C2 vs. 113.6°). The angles at N1 are 111.5° (C1−N1−C3) and 121.7° (C1−N1−C6), as compared to 115.6° and 113.1° of the corresponding angles in free L_{BY} — coordination of the hydroxyethyl arms to Cu^{II} can only be achieved by moving the arms towards the coordination centre.

Antimicrobial Activity Studies

Since only a few recent reports exist on the antifungal activities of macrocycles and their complexes,[13,15] it ap-

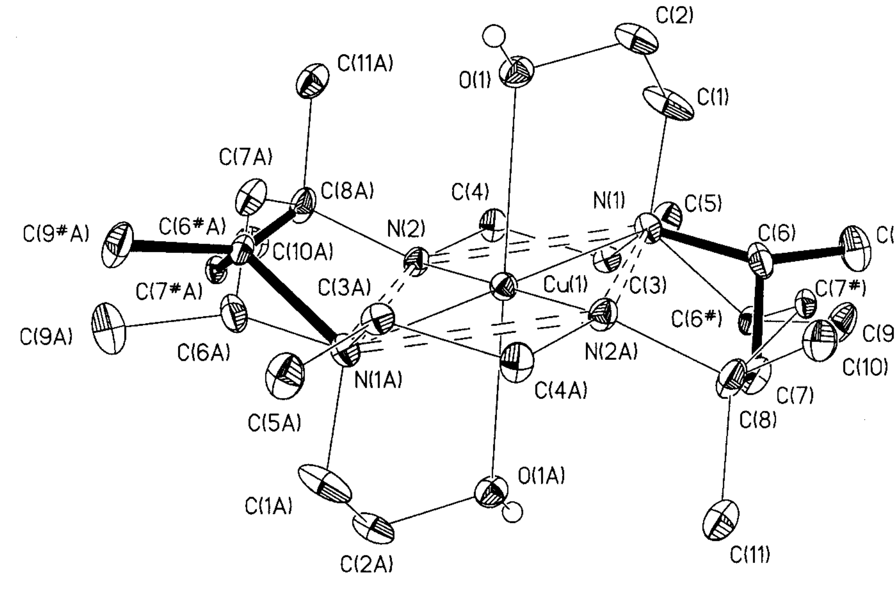

Figure 2. ORTEP plot (30% probability level), including disorder information, of $[Cu(L_{AY})]^{2+}$; "A" refers to symmetry related atoms, # and bold bonds to disordered regions; the plane spanned by the four nitrogen donors is emphasized by dashed lines; selected bond lengths (Å) and angles (°): Cu−N1 2.157(3), Cu−N2 1.992(3), Cu−O1 2.432(3), O1−C2 1.419(6); N1−Cu−N2 85.96(12), N1−Cu−N2A 94.04(12), N1−C1−C2 116.4(4), C2−O1−Cu 106.7(2) N1−Cu−O1 76.30(11), N1A−Cu−O1 103.70(11), N2−Cu−O1 94.46(12), N2A−Cu−O1 85.54(12)

Table 4. In vitro antifungal activities of ligands and their metal complexes

	Inhibition of mycelial growth (%)				
	Macrophomina phaseolina	*Alternaria alternata*	*Fusarium equiseti*	*Colletotrichum corcolei*	*Botrgodiplodia theobromal*
L_{BY}	52.00	36.00	38.68	39.69	47.58
L_{AY}	40.40	37.00	36.87	39.42	32.98
$[CuL_{BY}][ClO_4]_2$	32.00	21.22	27.00	2.58	31.36
$[CuL_{AY}][ClO_4]_2$	51.00	36.50	22.60	35.00	22.08
$[NiL_{AY}][ClO_4]_2$	13.00	0.00	0.00	3.50	31.00

peared interesting to see whether the compounds involved in the present study exhibit any such activity. We therefore investigated the antifungal potential of the ligands L_{BY} and L_{AY}, and their Cu^{II} and Ni^{II} complexes against five selective phytopathogenic fungi — (i) *Macrophomina phaseolina*, (ii) *Alternaria alternata*, (iii) *Fusarium equiseti*, (iv) *Colletotrichum corcolei*, and (v) *Botrgodiplodia theobromal*. It is evident from the results (Table 4) that the macrocycles and their complexes under investigation show some antifungal behaviour, which is more pronounced against *M. phaseolina* than against the other four organisms. The activity decreases upon coordination of the ligands to Cu^{II} and Ni^{II} in most cases, with the nickel complex showing the lowest activity. It has been noted that the N-substituted ligands (such as L_{BY}) exhibit a higher rate of inhibition on mycelial growth than their parent ligands (such as L_B).[13] The antifungal potential of the coordinated *N*-substituted ligands thus compares to that of the parent ligands; it also compares to the activities of copper[13] and nickel complexes[16] of the parent L_B and L_C.

Antibacterial activities of the macrocycles and their complexes have not been studied so far. Here, we report on the antibacterial activities against *Salmonella typhi*, *Shigella dysenteriae*, *Escherichia coli* and *Bacillus cerelus*. The results are contained in Table 5, which shows that the ligands do not exhibit any antibacterial activity, although some activity is noted for the complexes. Hence, unlike their behaviour towards fungi, some of the complexes exhibit higher antibacterial activities than their corresponding ligands. For a clear understanding, however, of the differentiation in function towards microorganisms, additional systematic studies will be necessary.

Table 5. Antibacterial activities of ligands and their metal complexes[a]

	Salmonella typhi	*Shigella dysenteriae*	*Escherichia coli*	*Bacillus cerelus*
L_{BY}	0	0	0	0
L_{AY}	0	0	0	0
$[CuL_{BY}][ClO_4]_2$	8	7	0	0
$[CuL_{AY}][ClO_4]_2$	12	14	3	0
$[NiL_{AY}][ClO_4]_2$	6	11	10	21

[a] Diameter of zone of inhibition in mm after 24 hours (see Exp. Sect. for details).

Conclusion

Two new tetraaza macrocyclic ligands belonging to the Me$_8$[14]ane family, and carrying pendent 2-hydroxyethyl substituents (Y) on two of the nitrogen functions, have been obtained by reacting the basic tetraaza ligands L_B and L_C with ethylene oxide. In the case of diaxial-diequatorial (with respect to the four methyl groups attached to chiral carbons) L_B as the starting product, the diaxial-diequatorial ligand L_{BY} is formed. When the reaction is carried out with axial-triequatorial L_C, a configurational change to all-equatorial L_{AY} was observed. With Ni^{II}, L_{BY} yields a square-planar complex $[Ni(L_{BY})]^{2+}$, where the hydroxyethyl functions are coordinatively inert towards Ni^{II}. With Cu^{II}, however, the octahedral complexes $[Cu(L)]^{2+}$ ($L = L_{BY}$ and L_{AY}) are formed, in which the OH functions weakly coordinate in the axial positions [Cu−O = 2.432(3) Å]. The counterion in the Ni and Cu complexes is ClO_4^-; the ionic nature has been confirmed by conductivity measurements in acetonitrile. In water, $[Cu(L)]^{2+}$ converts to $[Cu(L)(H_2O)_2]^{2+}$, whereas in chloroform the axial positions are occupied by perchlorate — the neutral complex $[Cu(L)(ClO_4)_2]$ is formed. Contrasting the ligands, the complexes show some anti-bacterial activity, while the anti-fungal activity of the complexes is generally lower than that of the ligands.

Experimental Section

Materials and Equipment: All chemicals were of analytical reagent grade and used without further purification. Synthesis of the parent ligand 3,10-*C*-*meso*-Me$_8$[14]diene dihydroperchlorate, reduction of this diene with $NaBH_4$ and separation into the three isomers of Me$_8$[14]ane (L_A, L_B and L_C) was carried out according to literature procedures.[4,17]

Caution*: *Perchlorates can be explosive in the presence of organic materials.

Microanalyses (C,H,N) were carried out by the combustion method at the Analytical Section of the Chemistry Department, University of Hamburg. For nickel and copper, standard titrimetric methods have been employed.
Infrared spectra were taken as KBr pellets in the range 4000−400 cm^{-1} on a Perkin−Elmer 883 infrared spectrophotometer. Electronic absorption spectra were recorded on a Schimadzu UV/Visible spectrophotometer. The mass spectral measurement of the li-

gands was carried out with the help of a Varian MAT 311A (70 eV, EI) instrument. ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz Varian Gemini instrument. Conductance measurements of the metal complexes were done in water, acetonitrile and chloroform solutions, using a HANNA instrument equipped with a HI 8820N conductivity cell. Magnetic measurements were carried out at room temperature with a Gouy balance, calibrated against Hg[Co(NCS)$_4$]; susceptibilities were corrected for diamagnetic increments.

Ligand Syntheses: Ligands were synthesised by modified literature procedures for analogous, N-pendent ligands.[8]

***trans*-4,11-Bis(2-hydroxyethyl)-3,5,7,7,10,12,14,14-octamethyl-1,4,8,11-tetraazacyclotetradecane (L_{BY}):** L_B (0.312 g, 1.0 mmol) was suspended in 25 mL of distilled water and the temperature was maintained at 16 ± 2 °C. The mixture was stirred while a gentle stream of ethylene oxide was passed through the suspension for 5 h. The reaction mixture became milky and then oily. Undissolved compounds were removed by filtration and the clear filtrate was extracted with 200 mL (four 50 mL portions) of chloroform. On evaporation of the chloroform extract, a sticky material was obtained, which was washed three times with 2 mL portions of methanol to give L_{BY} as a crude, white solid. This was re-crystallised from 10 mL of a 1:2 chloroform/methanol mixture and dried in vacuo over silica gel to yield pure L_{BY}. Melting point: 175 °C. Yield 0.202 g (50%). $C_{22}H_{48}N_4O_2$ (400.65): calcd. C 65.95, H 12.08, N 13.98; found C 65.86, H 11.95, N 13.88.

***trans*-4,11-Bis(2-hydroxyethyl)-3,5,7,7,10,12,14,14-octamethyl-1,4,8,11-tetraazacyclotetradecane (L_{AY}):** L_{AY} was prepared analogously to L_{BY} from L_C (0.312 g, 1.0 mmol) and ethylene oxide at a temperature of 10 ± 2 °C. Evaporation of the chloroform left behind a pasty substance, which was dissolved in 10 mL of methanol and filtered. The filtrate, on evaporation, yielded white, solid L_{AY}, which was re-crystallised three times from 10 mL portions of diethyl ether and dried under vacuum over silica gel. Melting point: 160 °C. Yield 0.22 g (50%). $C_{22}H_{48}N_4O_2$ (400.65): calcd. C 65.95, H 12.08, N 13.98; found C 65.79, H 11.91, N 14.06.

[NiL_{BY}][ClO$_4$]$_2$: L_{BY} (0.400 g, 1.0 mmol) and nickel(II) acetate (0.256 g, 1.05 mmol) tetrahydrate were dissolved separately in 50 mL of cold, dry methanol. The ligand solution was added dropwise to the boiling nickel(II) acetate solution with stirring. The reaction mixture was heated on a steam bath for one hour, and the volume reduced to 20 mL. An orange colour developed. After adding 0.5 g of lithium perchlorate trihydrate, the solution was heated for another 10 min and allowed to stand for about 2 h. The yellow product [NiL_{BY}][ClO$_4$]$_2$ was filtered off, washed with methanol and diethyl ether, and dried in vacuo. Yield 0.165 g (25%). $C_{22}H_{48}Cl_2N_4NiO_{10}$ (658.24): calcd. C 40.14, H 7.35, N 8.51, Ni 8.92; found C 39.88, H 7.30, N 8.48, Ni 8.88.

[CuL_{BY}][ClO$_4$]$_2$: L_{BY} (0.40 g, 1.0 mmol) and copper(II)perchlorate hexahydrate (0.371 g, 1.0 mmol) were dissolved separately in 25 mL of dry, hot methanol and mixed while hot. A pink colour appeared. The volume was reduced to 20 mL by heating the mixture on a water bath. On cooling, pink [CuL_{BY}][ClO$_4$]$_2$ crystallised out, which was separated by filtration, washed with methanol and re-crystallised from 10 mL of acetonitrile/methanol (1:2). The product was dried in a vacuum desiccator over silica gel. Yield 0.221 g (33%). $C_{22}H_{48}Cl_2CuN_4O_{10}$ (663.09): calcd. C 39.85, H 7.30, N 8.45, Cu 9.58; found C 39.80, H 7.32, N 8.36, Cu 9.49.

[CuL_{AY}][ClO$_4$]$_2$: L_{AY} (0.40 g, 1.0 mmol) and copper(II)perchlorate hexahydrate (0.371 g, 1.0 mmol) were dissolved separately in 20 mL of dry, hot methanol. The solutions were mixed while hot. The deep-blue reaction mixture was heated on a water bath to reduce the volume to 10 mL. On cooling, a blue solid precipitated out, which was separated by filtration and re-crystallised from 10 mL of acetonitrile/methanol (1:1), and dried in vacuo over silica gel. Yield 0.331 g (50%). $C_{22}H_{48}Cl_2CuN_4O_{10}$ (663.09): calcd. C 39.85, H 7.30, N 8.45, Cu 9.58; found C 39.79, H 7.24, N 8.43, Cu 9.48.

Table 6. Structure and refinement data for L_{BY} and [Cu(L_{AY})][ClO$_4$]$_2$

	L_{BY}	[Cu(L_{AY})][ClO$_4$]$_2$
Empirical formula	$C_{22}H_{48}N_4O_2$	$C_{22}H_{48}Cl_2CuN_4O_{10}$
Molecular mass (g·mol^{-1})	400.64	663.08
Temperature (K)	153(2)	293(2)
Crystal system	monoclinic	orthorhombic
Space group	$P2_1/c$	$Pbca$
a (Å)	18.9914(9)	12.0059(10)
b (Å)	12.2427(6)	14.2108(12)
c (Å)	10.2633(5)	17.4931(14)
β (°)	96.3670(10)	
Cell volume (Å^3)	2371.6(2)	2984.6(4)
Z	4	4
Calculated density (g·cm^{-3})	1.122	1.476
Absorption coefficient (mm^{-1})	0.072	0.968
F(000)	896	1404
Crystal size (mm)	0.9 × 0.7 × 0.2	0.3 × 0.3 × 0.2
θ range for data collection (°)	1.08 to 25.00	2.33 to 25.06
Index ranges	$-22 \le h \le 22$, $-14 \le k \le 14$, $-12 \le l \le 12$	$-14 \le h \le 14$, $-16 \le k \le 16$, $-20 \le l \le 20$
Reflections collected	43378	23697
Independent reflections	4171 [R(int) = 0.0536]	3422 [R(int) = 0.0423]
Completeness to theta = 32.56°	99.9%	99.7%
Goodness-of-fit on F^2	1.082	1.040
Final R_{int} [$I > 2\sigma(I_0)$]	$R1 = 0.0494$, $wR2 = 0.1277$	$R1 = 0.0693$, $wR2 = 0.1988$
R_{int} (all data)	$R1 = 0.0540$, $wR2 = 0.1316$	$R1 = 0.0929$, $wR2 = 0.2142$
Largest diff. peak and hole (e·Å^{-3})	0.391 and −0.536	0.622 and −1.769

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Crystals of $[CuL_{AY}][ClO_4]_2$ suitable for the X-ray diffraction study were prepared by slow evaporation of acetonitrile-methanol solution of the complex.

X-ray Crystallographic Determination: X-ray structure analyses were performed with Mo-K_α irradiation ($\lambda = 0.71073$ Å, graphite monochromator), on a Smart Apex CCD diffractometer. The hydrogen atoms of the hydroxy groups of L_{BY} and $[Cu(L_{AY})][ClO_4]_2$ and the NH groups of $[Cu(L_{AY})][ClO_4]_2$ were found; other H atoms were calculated at their idealized positions and included in the last cycles of refinement. Absorption corrections were carried out automatically by Mult Scan. Crystal data and details of the data collection and refinement are collated in Table 6.
CCDC-235762 (for L_{BY}) and -235880 (for $[Cu(L_{AY})][ClO_4]_2$) contain the supplementary crystallographic data of this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving/html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).

Antimicrobial Activity: The in vitro antifungal activities of the compounds against selected phytopathogenic fungi were assessed by the poisoned food technique. Potato Dextros Agar (PDA) was used as a growth medium. DMF was used as the solvent to prepare solutions of the compounds. The solutions were then mixed with the sterilized PDA so as to maintain concentrations of the compounds of 0.01%. 20 mL portions of this mixture were poured into petri dishes. After the medium had solidified, a 5 mm mycelial disc of the fungus was placed in the centre of each assay plate, including a control. Linear growth of the fungus (in mm) was noted after five days of incubation at 25 ± 2 °C.
The antibacterial activities of the test materials were measured by the disc diffusion method. Paper discs of 6 mm diameter, and petri dishes (70 mm in diameter) were used throughout. Pour plates were prepared from sterilized molten NA (Nutrient Agar) at 45 °C. After solidification of the pour plates, suspensions of the test organisms were spread uniformly over the pour plate with a sterilised glass rod. After soaking the paper discs with the test chemicals (1% in $CHCl_3$ solutions), they were placed in the centre of the inoculated pour plate. A control plate was maintained in each case with $CHCl_3$. The plates were kept for 4 h at low temperature (4 °C) in order to allow the test chemicals to diffuse from the paper disc to the surrounding medium. The plates were then incubated at 35 ± 2 °C for growth of the test organisms, and checked at 24-hour intervals. The antibacterial activity was expressed in terms of the diameter (in mm) of the zone of inhibition. Each experiment was repeated three times.

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[1] D. G. Pillsbury, D. H. Bush, *J. Am. Chem. Soc.* **1976**, *98*, 7836.
[2] W. P. Schammel, K. S. B. Mertes, G. G. Christoph, D. H. Bush, *J. Am. Chem. Soc.* **1979**, *101*, 1622.
[3] [3a] R. W. Hay, R. Bembi, *Inorg. Chim. Acta* **1982**, *65*, L227. [3b] C. M. Madeyski, J. P. Micheal, R. D. Hancock, *Inorg. Chem.* **1984**, *23*, 1487. [3c] K. P. Wainwright, *J. Chem. Soc., Dalton Trans.* **1983**, 1149. [3d] P. Clarke, S. F. Lincoln, K. P. Wainwright, *Inorg. Chem.* **1991**, *30*, 134.
[4] T. G. Roy, R. Bembi, *J. Bangladesh Chem. Soc.* **2002**, *15*, 23; *Chem. Abstr.* **2003**, *139*, 230266.
[5] R. Bembi, S. M. Sondhi, A. K. Singh, R. Singh, T. G. Roy, A. K. Jhanji, J. W. Lown, R. G. Ball, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3701.
[6] T. G. Roy, S. K. S. Hazari, B. K. Dey, H. A. Miah, E. R. T. Tiekink, *Acta Crystallogr.* **2001**, *E57*, 524.
[7] H. A. Miah, PhD Thesis, Department of Chemistry, Chittagong University, Bangladesh, **2003**.
[8] R. W. Hay, D. M. S. Clark, *Inorg. Chim. Acta* **1984**, *83*, L23.
[9] R. M. Silverstein, *Mass Spectrometry*, John Wiley & Sons, New York, **1967**, 2nd ed., pp. 4−63.
[10] H. Budzikiewicz, C. Dierassi, D. H. Williams, *Interpretation of Mass Spectra of Organic Compounds*, Holden-Day Inc., San Francisco, **1964**, pp. 63−110.
[11] T. G. Roy, R. Bembi, S. K. S. Hazari, B. K. Dey, T. K. Acharjee, E. Horn, E. R. T. Tiekink, *J. Coord. Chem.* **2002**, *55*, 853.
[12] R. Bembi, M. G. B. Drew, R. Singh, T. G. Roy, *Inorg. Chem.* **1991**, *30*, 1403.
[13] S. K. S. Hazari, T. G. Roy, B. K. Dey, S. C. Das, E. R. T. Tiekink, *Metal-Based Drugs* **1997**, *4*, 255.
[14] R. Bembi, R. Singh, T. G. Roy, A. K. Jhanji, *J. Coord. Chem.* **1985**, *14*, 119.
[15] T. G. Roy, S. K. S. Hazari, B. K. Dey, S. Chakraborty, E. R. T. Tiekink, *Metal-Based Drugs* **1997**, *6*, 345.
[16] T. K. Acharjee, M. Sc. Thesis, Department of Chemistry, Chittagong University, **2000**.
[17] N. F. Curtis, D. A. Swann, T. N. Waters, I. E. Maxwell, *J. Am. Chem. Soc.* **1969**, *91*, 4588.

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