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Two new *trans*-disubstituted cyclam ligands; 1,8-di(6-hydroxymethylpyridin-2-ylmethyl)-1,4,8,11-tetraazacyclotetradecane (**5**) and 1,8-dimethyl-4,11-di(6-hydroxymethylpyridin-2-ylmethyl)-1,4,8,11-tetraazacyclotetradecane (**6**); have been synthesized and characterized. The crystal structures of ligand **6** and its Ni(II) and Co(II) complexes have been determined. Crystal data are given for **6**, space group,  $P2_1/c$ ,  $a = 11.095(6) \text{ \AA}$ ,  $b = 9.467(5) \text{ \AA}$ ,  $c = 13.283(8) \text{ \AA}$ ;  $\beta = 106.95(5)^\circ$ ,  $Z = 2$ ,  $R = 0.0715$ ; for  $[\text{Ni } \mathbf{6}](\text{ClO}_4)_2$ , space group  $P2_1/c$ ,  $a = 9.4848(14) \text{ \AA}$ ,  $b = 33.941(6) \text{ \AA}$ ,  $c = 9.793(2) \text{ \AA}$ ,  $\beta = 95.264(14)^\circ$ ,  $Z = 4$ ,  $R = 0.0567$ ; for  $[\text{Co } \mathbf{6}](\text{ClO}_4)_2$ , space group,  $P2_1/c$ ,  $a = 9.440(6) \text{ \AA}$ ,  $b = 33.848(13) \text{ \AA}$ ,  $c = 9.820(3) \text{ \AA}$ ,  $\beta = 95.16(3)^\circ$ ,  $Z = 4$ ,  $R = 0.0718$ . In both complexes, the metal atoms are six-coordinate with only one of the pendants interacting with the central metal atom and the other pendant remaining uncoordinated.

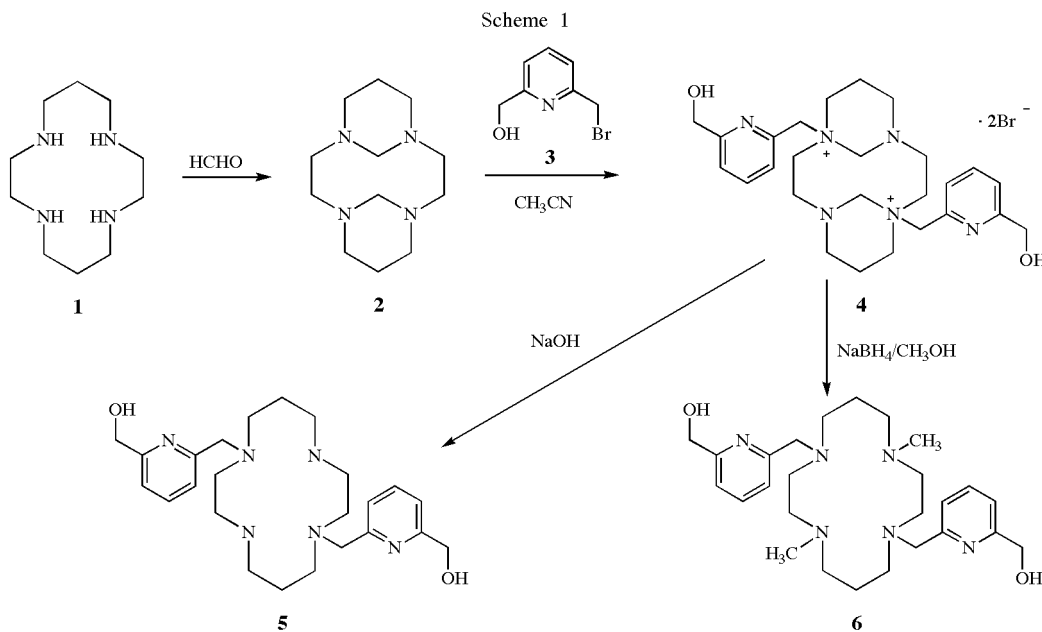
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### Introduction.

The design and synthesis of polyazamacrocyclic ligands have been the subject of growing interest during past few years due to their ability to form stable complexes with different metal ions, especially the transition and post-transition metal ions [1-4]. Applications of these chelating ligands have been developed rapidly in areas such as chemistry and biochemistry, analogs of enzymes, catalysis, purification of waste waters, radiochemical agents, selective coordination of dioxygen from air and potent inhibitors of HIV [5-8]. The number and nature of the *N*-substituents can increase selectivity for metal chelation as well as the stability of the formed complexes. The

polyazamacrocyclic ligand 1,4,8,11-tetraazacyclotetradecane (cyclam) has been extensively studied, either as a simple ligand or as an *N*-substituted ligand [9-14].

To date, numerous methods for the synthesis of poly-*N*-functionalized cyclams have been described [15-18]. Moreover, various methods for the synthesis of mono-*N*-functionalized cyclams have been reported [19-23]. On the other hand, dissymmetric *trans-N,N'*-difunctionalized cyclam ligands have been less studied due to difficulties encountered in their preparation. Recently, a convenient three-step protocol for the preparation of *trans*-disubstituted cyclams was developed by Guilard and coworkers [24]. Herein, we report the synthesis of two new *trans*-disub-



Synthesis of cyclam derivatives **5** and **6**

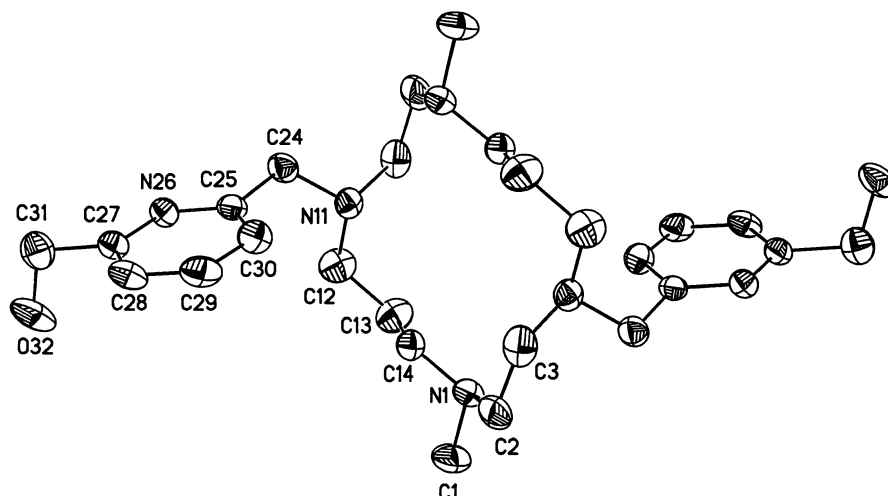


Figure 1. The crystal structure of **6** is shown. Hydrogen atoms were omitted for clarity. The thermal ellipsoids were drawn at the 30% probability level.

stituted cyclam ligands **5** and **6** (Scheme 1) appended with two 6-hydroxymethylpyridin-2-ylmethyl side arms using the method developed by Guilard and coworkers. We also report the crystal structures of 1,8-dimethyl-4,11-di(6-hydroxymethylpyridin-2-ylmethyl)-cyclam ligand (Figure 1) and its Co(II) and Ni(II) complexes. In both complexes, the metal atoms (Co and Ni) are six-coordinate with only one of the pendants interacting with the central metal atoms and the other pendant remaining uncoordinated

## Results and Discussion.

### Synthesis.

The synthetic route to ligands 1,8-di(6-hydroxymethylpyridin-2-ylmethyl)-1,4,8,11-tetraazacyclotetradecane (**5**) and 1,8-dimethyl-4,11-di(6-hydroxymethylpyridin-2-ylmethyl)-1,4,8,11-tetraazacyclotetradecane (**6**) is outlined in Scheme 1. Key intermediate **2** was prepared from formaldehyde and cyclam [24]. Treatment of **2** with

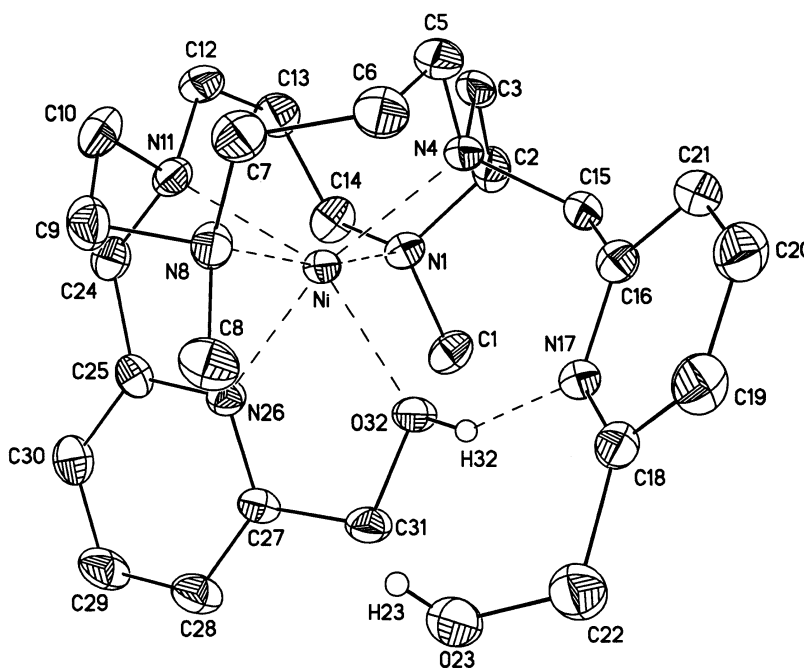


Figure 2. The crystal structure of  $[\text{Ni}_6](\text{ClO}_4)_2$ . Hydrogen atoms, the disordered oxygen O23' and the perchlorate ions were omitted for clarity. The thermal ellipsoids were drawn at the 30% probability level.

2-(bromomethyl)-6-(hydroxymethyl)-pyridine (**3**) [25] in acetonitrile gave disubstituted macrotricyclic salt **4** in a 90% yield. Ligand **5** was obtained in quantitative yield after basic hydrolysis of **4** in 3 M sodium hydroxide at room temperature. Reduction of **4** with sodium borohydride gave ligand **6** in a 90% yield.

The Ni(II) and Co(II) complexes of ligand **6** were obtained by the reaction of ligand **6** with Ni(II) and Co(II) perchlorate hexahydrate in acetonitrile.

#### Discussion of the Structures.

The solid state structures of **6** and [Ni**6**](ClO<sub>4</sub>)<sub>2</sub> are shown in Figures 1 and 2 respectively. The lattice parameters, which are included in Table 1, indicate that the Ni<sup>2+</sup> and Co<sup>2+</sup> complexes are isomorphous. This relationship was expected because the coordination properties and the covalent radii of Ni(II) and Co(II) are similar. Therefore only the Ni complex will be discussed, though some data for the Co complex are included in the tables. Molecule **6** contains a crystallographic inversion center located at 0.5, 0.0, 0.5. The molecule has a planar, extended conforma-

tion. The inversion center requires that the four nitrogen atoms of the ring lie in the same plane. The N1-N1a interatomic distance is significantly longer (5.551 Å) than the N11-N11a (4.920 Å) interatomic distance. The unusual atom labeling scheme for **6** was selected in order to make comparison of **6** with [Ni(**6**)](ClO<sub>4</sub>)<sub>2</sub> easier. The sidearms of neighboring **6** molecules are linked together by two hydrogen bonds (see Figure 3) which form an interaction similar to that found in many carboxylic acids. The sidearms of each molecule furnish a donor atom (O32) and an acceptor atom (N26). There is another inversion center relating the neighboring molecules located at 1.0, 0.5, 0.5, which causes the double linkage. The hydrogen bond data are contained in Table 2. There are linkages at both ends of each molecule. As a result of these interactions, long chains of molecules are formed.

The conformation of the ligand changes significantly upon complexation with a cation with the complex being much more compact than the uncomplexed ligand, which is shown by comparing the structures in Figures 1 and 2. It might be expected that the four nitrogen atoms of the

Table 1  
Crystal Data and Experimental Details

Compound	<b>6</b>	[Ni <b>6</b> ](ClO <sub>4</sub> ) <sub>2</sub>	[Co <b>6</b> ](ClO <sub>4</sub> ) <sub>2</sub>
Formula	C <sub>26</sub> H <sub>42</sub> N <sub>6</sub> O <sub>2</sub>	[Ni(C <sub>26</sub> H <sub>42</sub> N <sub>6</sub> O <sub>2</sub> )](ClO <sub>4</sub> ) <sub>2</sub>	[Co(C <sub>26</sub> H <sub>42</sub> N <sub>6</sub> O <sub>2</sub> )](ClO <sub>4</sub> ) <sub>2</sub>
Formula weight	470.66	728.27	728.49
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	P2 <sub>1</sub> /c	P2 <sub>1</sub> /c	P2 <sub>1</sub> /c
a(Å)	11.095(6)	9.4848(14)	9.440(6)
b(Å)	9.467(5)	33.941(6)	33.848(13)
c(Å)	13.283(8)	9.793(2)	9.820(3)
β(°)	106.97(5)	95.264(14)	95.16(3)
V(Å <sup>3</sup> )	1334.5(13)	3139.3(9)	3125(2)
Z	2	4	4
F(000)	512	1528	1524
D <sub>calc.</sub> (g cm <sup>-3</sup> )	1.171	1.541	1.548
Crystal size (mm)	0.30x0.25x0.15	0.3x0.3x0.2	0.5x0.3x0.2
μ(mm <sup>-1</sup> )	0.076	0.853	0.785
Temperature	293(3)	293(3)	293(3)
2θ range	5.36-46.04	4.32-45.00	4.82-50.00
Total data	2218	4531	5757
Independent data	1836(R <sub>int</sub> =0.0492)	4073(R <sub>int</sub> =0.0375)	5421(R <sub>int</sub> =0.0532)
Parameters	158	416	416
Goodness of fit, F <sup>2</sup>	1.067	1.028	1.028
R[>2σ(I)]	0.0715	0.0567	0.0718
R(all data)	0.1665	0.0944	0.1516
Largest difmap peak and hole (eÅ <sup>-3</sup> )	0.195, -0.165	0.707, -0.383	0.819, -0.403

Table 2  
Hydrogen Bond Data

Compound	D	H	A	D-H(Å)	H...A(Å)	D...A(Å)	<D-H...A(°)
<b>6</b>	O32	H32	N26[a]	0.83	2.00	2.816	168
[Ni <b>6</b> ](ClO <sub>4</sub> ) <sub>2</sub>	O32	H32	N26	0.99	1.71	2.614	149
[Ni <b>6</b> ](ClO <sub>4</sub> ) <sub>2</sub>	O23	H23	O53	0.82	2.11	2.708	130
[Ni <b>6</b> ](ClO <sub>4</sub> ) <sub>2</sub>	O23'	H23'	O41	0.82	2.29	3.052	155

[a] N26 is in a symmetry related molecule.

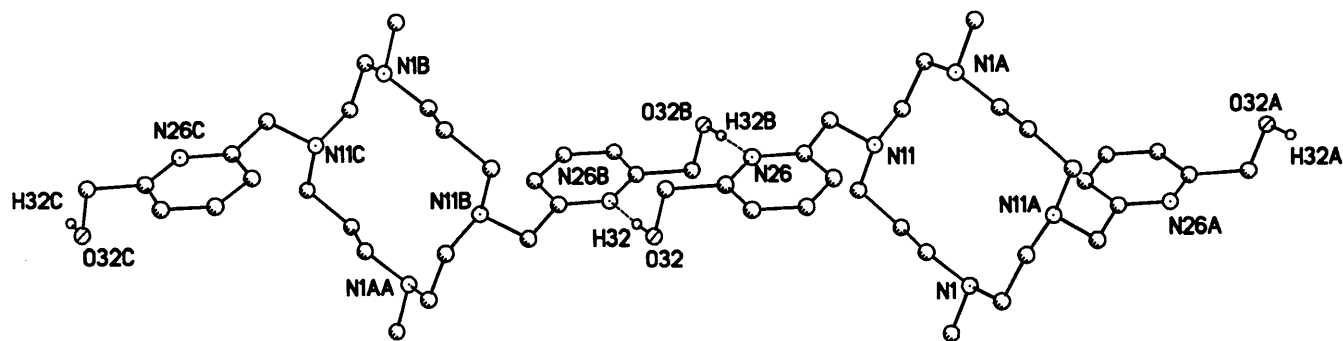


Figure 3. The drawing shows the hydrogen-bonding scheme, which links molecules of **6** together.

cyclam would occupy four sites of the octahedral Ni complex with the nitrogen or oxygen atoms of each arm occupying the other two sites. However, this is not the case. In the complex, only one arm is involved in the complexation as N26 and O32 of one sidearm completes the coordination of the nickel cation. The octahedral coordination is greatly distorted as the interatomic distances between atom pairs adjacent to each other in the complex range from 2.559 Å (N26...O32) to 3.776 Å (N4...N11). The interatomic distance range between opposite pairs of atoms is smaller, 4.119 Å (N4 to N26) to 4.368 Å (N1 to N8). Another interaction that contributes to the compact conformation of the structure is an intramolecular hydrogen bond that links O32, an atom of the sidearm in the coordination sphere of the Ni cation, to N17, the nitrogen atom of the non-coordinating sidearm. The disordered oxygen atom, O23 and O23', interact with two perchlorate oxygen atoms. The donor O23 interacts with O53 of one perchlorate while O23' interacts with O41 of the other perchlorate. Hydrogen bond data for **6** and [Ni**6**](ClO<sub>4</sub>)<sub>2</sub> are included in Table 2.

#### EXPERIMENTAL

The <sup>1</sup>H and <sup>13</sup>C nmr spectra were recorded at 200 or 300 MHz and 50 or 75 MHz, respectively, in deuterated chloroform or deuterium oxide solutions with tetramethylsilane as reference. Melting points were uncorrected. Hrms spectra were determined using the fast atom bombardment (fab) method. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Solvents and starting materials were purchased from commercial sources where available. Compounds **2** and **3** were synthesized as described in references 24 and 25.

Preparation of 1,8-Di(6-hydroxymethylpyridin-2-ylmethyl)-1,4,8,11-tetraazatricyclo[9.3.1.1<sup>4,8</sup>]hexadecan-1,8-dium Dibromide (**4**) (Scheme 1).

Compound **2** (1.00 g, 4.45 mmole) was dissolved in 30 ml of acetonitrile and two equiv. of **3** (1.80 g, 8.9 mmole) was rapidly added. The solution was stirred at room temperature overnight, the white precipitate was collected by filtration, washed with a small quantity of acetonitrile and dried under vacuum. This

crude compound was recrystallized in water to give 2.52 g (95%) of white crystals; <sup>1</sup>H nmr (D<sub>2</sub>O): δ 7.60-7.10 (m, 6H), 5.55 (d, 2H), 4.76 (d, 4H), 4.70 (s, 4H), 4.39 (t, 2H), 3.80-2.81 (m, 14 H), 2.70-2.30 (m, 4H), 1.87 (m, 2H).

Anal. Calcd. for C<sub>26</sub>H<sub>40</sub>N<sub>6</sub>O<sub>2</sub>Br<sub>2</sub>·2H<sub>2</sub>O : C, 47.00; H, 6.67. Found: C, 46.85; H, 6.91.

Preparation of 1,8-Di(6-hydroxymethylpyridin-2-ylmethyl)-1,4,8,11-tetraazacyclotetradecane (**5**) (Scheme 1).

Compound **4** (1.00 g, 1.60 mmole) was dissolved in 100 ml of an aqueous sodium hydroxide solution (3 M). After stirring for 3 hours at room temperature, the solution was extracted with chloroform (5 x 30 ml). The organic phases were collected, dried over anhydrous magnesium sulfate and concentrated under vacuum to give ligand **5** in a quantitative yield; mp 173-174°; <sup>1</sup>H nmr: δ 7.55 (t, 2H), 7.26 (d, 2H), 7.03 (d, 2H), 4.76 (br., 2H), 4.65 (s, 4H), 3.82 (s, 4H), 2.80 (br., 2H), 2.72-2.70 (m, 12H), 2.59 (t, 4H), 1.81 (m, 4H); <sup>13</sup>C nmr: δ 162.1, 158.9, 138.9, 123.7, 120.5, 65.9, 60.3, 55.1, 53.7, 50.4, 48.2, 26.7; hrms (fab) m/z: calcd. for C<sub>24</sub>H<sub>38</sub>N<sub>6</sub>O<sub>2</sub> (M+1)<sup>+</sup>: 443.3137, found: 443.3142.

Anal. Calcd. for C<sub>24</sub>H<sub>38</sub>N<sub>6</sub>O<sub>2</sub>: C, 65.13; H, 8.65. Found: C, 64.95; H, 8.87.

Preparation of 1,8-Di(6-hydroxymethylpyridin-2-ylmethyl)-4,11-dimethyl-1,4,8,11-tetraazacyclotetradecane (**6**).

Compound **4** (0.63 g, 1 mmole) was dissolved in 20 ml of ethanol/water (95:5), sodium borohydride (0.38 g, 10 mmole) was then added and the mixture was refluxed, for 3 hours. After cooling to room temperature, 10 ml of hydrochloric acid (3 M) was added. The mixture was concentrated to dryness and the residue was then dissolved in 100 ml of water and neutralized with concentrated potassium hydroxide (pH = 12). After extraction with chloroform (5 x 30 ml), the organic phases were collected, dried over anhydrous magnesium sulfate and concentrated under vacuum to give ligand **6** (90%); mp 137-138°; <sup>1</sup>H nmr: δ 7.65 (t, 2H), 7.48 (d, 2H), 7.11 (d, 2H), 4.73 (s, 4H), 4.20 (br., 2H), 3.75 (s, 4H), 2.71-2.43 (m, 16H), 2.12 (s, 6H), 1.68 (m, 4H); <sup>13</sup>C nmr: δ 161.7, 160.5, 138.9, 123.4, 120.3, 65.7, 61.8, 55.5, 54.9, 53.0, 52.1, 43.6, 24.8; hrms (fab) m/z: calcd for C<sub>26</sub>H<sub>42</sub>N<sub>6</sub>O<sub>2</sub>Na (M+Na)<sup>+</sup>: 493.3271; found: 493.3256. Crystals of this compound suitable for X-ray analysis were grown by slow evaporation of a dilute acetonitrile/ethanol solution (5:1) at room temperature.

Anal. Calcd. for C<sub>26</sub>H<sub>42</sub>N<sub>6</sub>O<sub>2</sub>: C, 66.35; H, 8.99. Found: C, 66.15; H, 8.76.

Preparation of [Ni(6)](ClO<sub>4</sub>)<sub>2</sub>.

A solution of Ni(ClO<sub>4</sub>)<sub>2</sub> · 6H<sub>2</sub>O (18.5 mg, 0.05 mmole) in 1 ml of acetonitrile was added to **6** (24.7 mg, 0.05 mmol) in 1 ml of acetonitrile at room temperature. Blue crystals of the complex suitable for X-ray analysis were obtained by slow evaporation of this solution to give 31.3 mg (86%).

Anal. Calcd. for C<sub>26</sub>H<sub>42</sub>N<sub>6</sub>O<sub>10</sub>Cl<sub>2</sub>Ni: C, 42.88; H, 5.81. Found: C, 43.04; H, 5.72.

Preparation of [Co(6)](ClO<sub>4</sub>)<sub>2</sub>.

This pink complex was obtained in a manner similar to that described for the above complex except that Co(ClO<sub>4</sub>)<sub>2</sub> · 6H<sub>2</sub>O was used instead of the nickel salt to give 29.9 mg (82%) of the complex.

Anal. Calcd for C<sub>26</sub>H<sub>42</sub>N<sub>6</sub>O<sub>10</sub>Cl<sub>2</sub>Co: C, 42.87; H, 5.81. Found: C, 43.02; H, 5.72.

## Crystal Data and Refinement.

The crystal data and experimental details for **6**, [Ni(6)](ClO<sub>4</sub>)<sub>2</sub> and [Co(6)](ClO<sub>4</sub>)<sub>2</sub> are listed in Table 1. Crystal and intensity data for the structures were obtained using a Bruker P4 automated diffractometer with graphite monochromated MoK $\alpha$  radiation ( $\lambda=0.71073\text{\AA}$ ). Additional crystal data, experimental details and tables of atomic parameters, bond lengths and bond angles are contained in the deposited data. The solid state structures **6** and the Co complex were solved using direct methods. The structure of **6** contains a center of inversion. It was apparent from the lattice parameters that the structures of the nickel and cobalt complexes were isomorphous (see Table 1). The structure of the Ni complex was determined by refining the atomic parameters obtained in the solution of the Co complex, substituting Ni for Co and using the intensity data obtained from a [Ni(6)](ClO<sub>4</sub>)<sub>2</sub> crystal. In both structures O23 was disordered. This disorder was resolved using difference maps. The occupancy parameters of the disordered atoms were refined to approximately 0.5 in both structures. The large anisotropic thermal parameters of the perchlorate oxygen atoms indicated that the perchlorate ions were slightly disordered. The disorder was not resolved in as much as it was not important to the purpose of the study.

The structures were refined using a full matrix, least-squares procedure on F<sup>2</sup>. All non-hydrogen atoms including the disordered oxygen atoms were refined anisotropically. Positions for all hydrogen atoms except those bonded to O32 in each structure were calculated. The positions for the H32 atoms, which were involved in hydrogen bonding, were located in the difference maps. All hydrogen atoms were allowed to ride on the heavy atoms to which they were bonded during the refinement process. Programs used to solve, refine and display the structures are contained in the SHELXTL PC program package. [26]

## Acknowledgment.

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## Supplementary Materials.

Atomic coordinates, displacement parameters, bond lengths and angles and additional experimental details have been deposited at the Cambridge Crystallographic Centre.

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