Proton-Ionizable Crown Compounds. 3. Synthesis and Structural Studies of Macrocyclic Polyether Ligands Containing a 4-Pyridone Subcyclic Unit [1]

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New proton-ionizable macrocyclic polyether ligands containing the 4-pyridone subcyclic unit have been prepared by reacting 4-THP blocked-2,6-pyridinedimethanol with various oligoethylene glycol ditosylates. The 18-crown-6 ligand containing the 4-pyridone subcyclic unit, **4**, forms stable complexes with alkali metal and organic ammonium cations. The crystal structure of **4** proves the 4-pyridone structural unit. The crystal structure of the potassium thiocyanate complex of **4** is also reported and shows the complex to contain the 4-hydroxypyridine unit.

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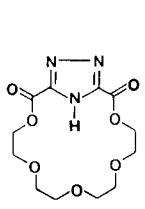
Introduction.

We are interested in the design of host molecules which show selectivity toward guest molecules and ions. Recently, we described the preparation of new macrocyclic compounds which contain ionizable protons as part of the macrocyclic ring [4,5]. Reference 4 gives a review of proton-ionizable macrocyclic ligands. Both the triazolo diester-18-crown-6 (**1**) [4] and 4-hydroxypyridino diester-18-crown-6 (**2**) [5] formed stable complexes with benzylamine where the ionizable proton was transferred to the amine. A disadvantage of diester crowns in many applications, such as transport in liquid membrane systems, is their instability either in aqueous base, in methanolic base or in acid solutions. In fact, we have shown that the transesterification procedure used to make the diester-crowns is a reversible process [6]. The series of non-ester proton-ionizable ligands reported here which contain the 4-pyridone subcyclic unit (**3-7**, Figure 1) are stable in acidic and basic media.

Figure 1.Structures of Compounds



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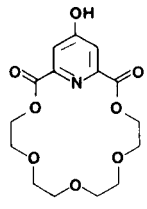

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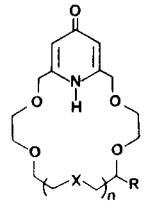
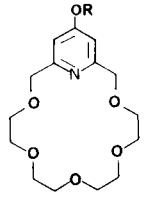


3, X = O, n = 0, R = H
4, X = O, n = 1, R = H
5, X = O, n = 2, R = H
6, X = O, n = 1, R = octyl
7, X = S, n = 1, R = H



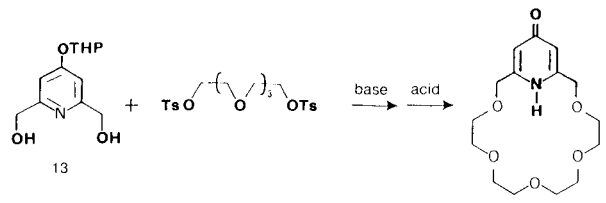
8, R = n-octyl
9, R = allyl

Two communications report the synthesis of compounds **4** and **8**, the pK_a(water) values for H_2L^+ and HL for **4**, the crystal structure of **4**, and transport data for **4** and **6** using a potassium hydroxide-dichloromethane-water liquid membrane system [7,8]. It was found that compound **6** failed to transport potassium ions at *p*H values below about 12 but was very effective in transporting potassium ions at *p*H levels above 12 [8]. Since the pK_a value of **4** is 10.98 [7], it is assumed that potassium ion transport by **6** above *p*H 12 is coupled with an opposite flow of protons with the major driving force being the formation of water at the source phase-dichloromethane interface. Compound **6** was effective in transporting potassium ions selectively over other alkali metal cations from 1*M* metal hydroxide solutions.

This paper describes the synthesis of compounds **3-9**, together with structural studies of the interaction of potassium thiocyanate and benzylammonium perchlorate with **4**. In addition, qualitative observations are made for several other cation-macrocycle interactions.

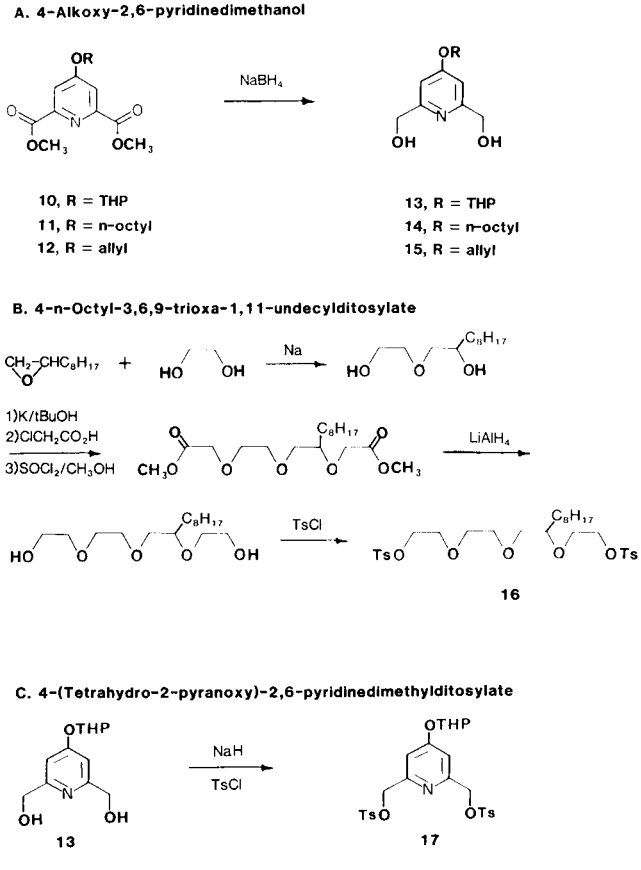
Results and Discussion.

Compounds **3-7** were prepared by the treatment of the appropriate oligoethylene glycol ditosylate with 4-(tetrahydro-2-pyranoxy)-2,6-pyridinedimethanol (**13**) followed by an acid hydrolysis as shown below. The alternate reaction of the ditosylate derivative of 4-THP blocked pyridinedimethanol (compound **17**, Figure 2C) with tetraethylene glycol was also a successful method to prepare **4**. Compounds **8** and **9** were prepared from the corresponding 4-octoxy- and 4-allyloxy-2,6-pyridinedimethanol starting



materials. The product yields varied from 11 to 45 percent for these cycloaddition reactions. Compound **8** was also prepared by treatment of compound **4** with *n*-octyl bromide in base [7]. The starting 2,6-pyridinedimethanol and ditosylate compounds were prepared as shown in Figure 2. The structures proposed for the macrocyclic compounds are consistent with data obtained from ir and nmr spectra, combustion analyses and, in the case of **4**, crystal-structure determinations. A band at 1640 cm^{-1} in the ir for **3-7** is indicative of the pyridone carbonyl function. Ligands **3-7** also have peaks at about δ 6.2 indicative of the two ring protons in a pyridone ring. Ligands **8** and **9** exhibit the usual aromatic protons at about δ 6.8.

Figure 2. Preparation of Starting Materials



The new macrocyclic compounds formed complexes with various cations. Indeed, the initial cyclization reaction yielded the potassium (or sodium in the case of **3**) tosylate complex of the 4-alkoxymacrocycle. The salt was removed by acid or by passing the complex through an alumina column. Compound **4** also formed stable complexes with benzylammonium perchlorate and 2-phenylethylammonium thiocyanate. In these cases the 1640 cm^{-1} ir band was no longer evident, indicating a change from the pyridone to the 4-hydroxypyridine structure. Unlike diester **2**, which formed complexes with amines [5], these new proton-ionizable ligands do not form stable complexes

Table 1

Bond Lengths (Å) and Angles (deg) of **4** (Figure 3) and the Potassium Thiocyanate Complex of **4** (Figure 4) and Potassium-heteroatom Distances of the Complex. Numbers in Parentheses are e.s.d. Values

Atom		**4**	Potassium Thiocyanate Complex of **4**	
1 2 3	1-2	1-2-3	1-2	1-2-3
N1 C2 C3	1.361(3)	116.2(2)	1.325(10)	116.7(7)
C2 C3 O4	1.494(3)	111.0(2)	1.510(10)	109.9(6)
C3 O4 C5	1.433(3)	113.0(2)	1.406(9)	110.8(6)
O4 C5 C6	1.425(3)	108.8(2)	1.425(9)	108.8(7)
C5 C6 O7	1.494(3)	109.7(2)	1.494(11)	107.9(6)
C6 O7 C8	1.421(3)	112.8(2)	1.419(10)	113.0(5)
O7 C8 C9	1.432(3)	112.8(2)	1.425(9)	108.5(6)
C8 C9 O10	1.505(4)	114.6(2)	1.504(12)	108.1(7)
C9 O10 C11	1.426(3)	113.6(2)	1.420(10)	111.3(6)
O10 C11 C12	1.410(4)	110.0(2)	1.418(10)	109.4(7)
C11 C12 O13	1.498(4)	110.0(2)	1.510(11)	106.3(6)
C12 O13 C14	1.433(3)	111.9(2)	1.424(9)	111.3(6)
O13 C14 C15	1.404(3)	111.5(2)	1.424(9)	107.6(6)
C14 C15 O16	1.503(4)	110.1(2)	1.486(11)	108.1(6)
C15 O16 C17	1.417(3)	112.3(2)	1.416(9)	113.3(5)
O16 C17 C18	1.426(3)	112.4(2)	1.376(9)	113.8(6)
C17 C18 N1	1.503(3)	115.5(2)	1.509(11)	116.4(7)
C18 N1 C2	1.356(3)	121.9(2)	1.335(9)	116.6(6)
N1 C2 CA3	[a]	124.2(2)	[a]	124.1(6)
C2 CA3 CA4	1.351(3)	122.2(2)	1.388(11)	118.6(7)
CA3 C2 C3	[a]	124.0(2)	[a]	119.2(7)
CA3 CA4 CA5	1.436(3)	114.3(2)	1.398(9)	117.5(7)
OA4 CA4 CA3	1.261(3)	122.4(2)	1.346(9)	121.7(7)
OA4 CA4 CA5	[a]	123.3(2)	[a]	119.2(7)
CA4 CA5 C18	1.441(3)	121.7(2)	1.378(11)	119.3(6)
CA5 C18 N1	1.352(3)	120.2(2)	1.384(11)	123.8(7)
CA5 C18 C17	[a]	124.3(2)	[a]	119.6(6)
HN1 N1 C2	0.90(2)	118(1)		
NH1 N1 C18	[a]	120(1)		
HOW1 OW HOW2	0.87(4)	105.(3)		
HOW2 OW HOW1	0.95(3)	[a]		
HOA4 OA4 CA4			1.10 [b]	118 [b]
S C N			1.618(9)	178.7(8)
C N			1.164(12)	
	K-O4	2.800(5)	K-N1	2.806(6)
	K-O7	2.783(5)	K-OA4	3.018(6) [c]
	K-O10	2.795(6)	K-S	3.355(4)
	K-O13	2.773(6)		
	K-O16	2.820(5)		

[a] Value reported previously in the table. [b] No e.s.d. values are reported as the positional parameters of HOA4 were not refined. [c] Distance to an atom of a symmetry related molecule.

Table II

Hydrogen Bond Data for **4** and the Potassium Thiocyanate Complex of **4**

D H A	Symmetry of A	D ··· A(Å)	H ··· A(Å)	D-H ··· A(deg.)
		4		
N1 HN1 O4	-x, 1-y, -z	2.870(3)	1.98(2)	172.2(2)
OW HOW1 O4A	x, y, z	2.851(3)	2.00(4)	169(3)
OW HOW2 O4A	1-x, .5+y, .5-z	2.845(3)	1.89(3)	172(3)
		Potassium Thiocyanate Complex of **4**		
OA4 HOA4 N	-x, 2-y, 2-z	2.682(10)	2.12 [a]	109 [a]

[a] No e.s.d. value listed as the positional parameters of HOA4 were not refined.

with amines. These results are not unexpected since the pK_a for the removal of the ionizable proton from **4** is 10.98 [7], indicating that **4** is a very weak acid and will not react with an amine base. McKervey and coworkers found that their phenolic macrocycles with a pK_a of 10.6 likewise did not form stable complexes with amines [9]. Their 4-nitro-substituted phenolic macrocycle with a pK_a of 6.6 did form stable complexes with amines as did our diester crown **2**, which has a pK_a of 8.49 [5].

The pK_a values for **2** and **4** (8.49 and 10.98 respectively) also suggest different structures for the pyridine ring portion in these two compounds. The pK_a for **4** is similar to that for 4-hydroxypyridine which exists in the 4-pyridone form. X-ray structure determinations show **2** to have the 4-hydroxypyridine structure [5] and **4** to have the 4-pyridone structure [7]. A crystal of the complex of benzylammonium perchlorate with **4** was prepared. However, the extreme disorder of the perchlorate anion group caused significant problems in the detailed structure analysis of that complex. It was possible to determine that the nitrogen of the ammonium group did lie above the ring and therefore was probably hydrogen bonded to the heteroatoms of the crown ether ring [10].

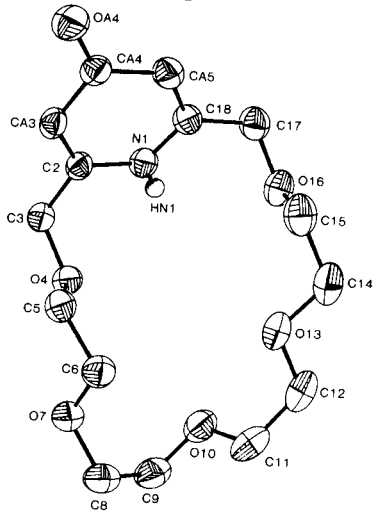


Figure 3. Computer Drawing of **4**. The Water of Hydration and All Hydrogen Atoms, Except HN1, Are Omitted for Clarity.

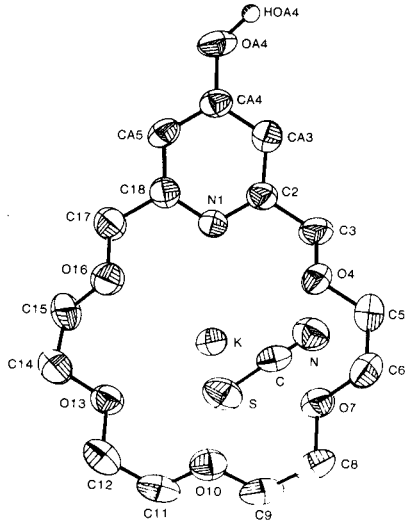


Figure 4. Computer Drawing of the Potassium Thiocyanate Complex of **4**. All Hydrogen Atoms, Except HOA4, Are Omitted for Clarity.

The structure of **4** and of the potassium thiocyanate complex of **4** as well as the atom labels of these compounds are shown in Figures 3 and 4. The bond distances and angles of the two compounds are compared in Table I. The interatomic distances from potassium ion to all atoms coordinated to that ion are also listed in that table. The potassium ion has 8-fold coordination, which includes the six heteroatoms of the crown ligand, the sulfur of the thiocyanate anion above the nearly planar hexagon of the heteroatoms, and OA4 of a neighboring molecule (-x, 1-y, 2-z) below the plane. The complex is unusual in that the coordination sphere of the potassium ion includes an atom of a neighboring complex. Unlike potassium thiocyanate complexes of other 18-crown-6 ligands [11-13], the nitrogen atom of the thiocyanate anion is not coordinated to the potassium ion, but rather is involved in a hydrogen bond with OA4 of a symmetry related molecule (-z, 2-y, 2-z). This hydrogen bond will be discussed below.

It is significant that the pyridine subunit of **4** is present as a pyridone (Figure 3), while the same subunit in the

complex of **4** and potassium thiocyanate is present as a 4-hydroxypyridine (Figure 4). The HOA4 of the complex was located in a difference map. This structural feature is also evident in the differences in bond lengths of the six membered units (see Table I). The C-O interatomic distance shows that a C-O double bond (1.261 Å) is present in **4** while a C-O single bond (1.346 Å) is present in the potassium thiocyanate complex. Also in the pyridone ring of **4**, the C-C bond distances show the presence of single and double bonds typical of the 4-pyridone, while the C-C bond lengths in the complex are nearly equal, indicating aromatic character. It is apparently energetically favorable for the hydrogen on N1 in **4** to be transferred to OA4 in the complex so that the metal ion can complex with all six heteroatoms of the ligand.

Table III

Crystal Data and Experimental Data

	4	Potassium Thiocyanate Complex of **4**
Formula	$C_{15}H_{23}NO_6 \cdot H_2O$	$C_{15}H_{23}NO_6 \cdot KSCN$
Mr	331.4	410.6
Crystal size (mm)	0.4 × 0.4 × 0.2	0.25 × 0.3 × 0.3
Space group	$P2_1/c$	$P2_1/c$
a (Å)	11.359(5)	12.935(10)
b (Å)	7.628(2)	8.923(5)
c (Å)	19.084(4)	17.688(16)
α (deg)	90	90
β (deg)	98.31(3)	100.55(6)
γ (deg)	90	90
V (Å^3)	1647	2007
Z	4	4
Dx (gcm^{-1})	1.34	1.36
Total unique reflections	2233	2949
unobserved, $I < 2\sigma(I)$	261	1413
unique obs. ref.	1971	1536
radiation	Cu	Mo
Sin θ/λ	0.55	0.65
Rm	0.07	0.02
R	0.045	0.068
Rw	0.069	0.076
Maximum and minimum peak in difference map (e Å^{-3})	+0.27, -0.18	+0.42, -0.29

Hydrogen bonding is of significant importance in linking molecules together in both compounds. As indicated above, in the complex of **4** there is a hydrogen bond between the nitrogen atom of thiocyanate anion and OA4 of another molecule. The molecules of **4** are linked by a water of hydration present in the structure and also by a hydrogen bond involving N1 and HN1 of one molecule and O4 of another molecule. The hydrogen bond data are included in Table II.

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Beckman Acculab 2 spectrometer. The proton nuclear magnetic resonance (nmr) spectra were obtained in a JEOL FX-90Q spectrometer. Crystal structure determinations were done on a Nicolet R3 autodiffractometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Molecular weights were obtained by osmometry on a Hitachi Perkin-Elmer Model 115 molecular weight apparatus. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Starting materials were purchased from commercial sources where available. All oligoethylene glycol tosylates except **17** were prepared by the reaction of the corresponding oligoethylene glycols with *p*-toluenesulfonyl chloride in pyridine [14] (see below for **16**). All other starting materials were prepared according to the following procedures (see Figure 2).

Table IV

Positional Paramaters (× 10^4) and Thermal Parameters (× 10^3) for **4** with e.s.d. Values in Parentheses. Hydrogen Atoms of the Polyether Ring Are Omitted

Atom	x	y	z	U	
N1	1656(2)	4526(2)	898(1)	38(1)	[a]
HN1	1092(19)	3963(28)	605(11)	47(6)	
C2	2002(2)	6130(3)	704(1)	35(1)	[a]
C3	1291(2)	6907(3)	60(1)	40(1)	[a]
O4	66(1)	7086(2)	151(1)	39(1)	[a]
C5	−114(2)	8326(3)	681(1)	41(1)	[a]
C6	−1384(2)	8252(3)	799(1)	47(1)	[a]
O7	−2134(1)	8785(2)	175(1)	51(1)	[a]
C8	−3372(2)	8709(4)	244(2)	61(1)	[a]
C9	−3920(2)	6961(4)	44(2)	61(1)	[a]
O10	−3371(1)	5536(2)	444(1)	56(1)	[a]
C11	−3671(2)	5427(4)	1134(1)	63(1)	[a]
C12	−3099(2)	3854(4)	1504(2)	65(1)	[a]
O13	−1835(1)	4083(2)	1643(1)	55(1)	[a]
C14	−1289(2)	2834(3)	2121(1)	57(1)	[a]
C15	43(2)	2905(3)	2176(1)	55(1)	[a]
O16	423(1)	1991(2)	1604(1)	47(1)	[a]
C17	1686(2)	1974(3)	1644(1)	49(1)	[a]
C18	2180(2)	3731(3)	1498(1)	39(1)	[a]
CA3	2904(2)	6960(3)	1110(1)	37(1)	[a]
HA3	3139	8092	968	43	
CA4	3522(2)	6206(3)	1748(1)	36(1)	[a]
OA4	4360(1)	6980(2)	2129(1)	47(1)	[a]
CA5	3087(2)	4517(3)	1918(1)	42(1)	[a]
HA5	3449	3936	2340	49	
OW	4688(2)	10366(3)	1575(1)	98(1)	[a]
HOW1	4661(30)	9289(48)	1708(17)	117(12)	
HOW2	5050(29)	10972(49)	1984(18)	117(12)	

[a] U_{iq} value which is one-third the trace of the orthogonalised U_{ij} tensor.

Dimethyl 4-Allyloxy-2,6-pyridinedicarboxylate (**12**).

A suspension of dimethyl chelidamate [5] (10.1 g, 4.78 × 10^{-2} mole), 10.1 g (7.31 × 10^{-2} mole) of potassium carbonate, and 10.0 ml (1.16 × 10^{-1} mole) of allyl bromide in 75 ml of acetone was refluxed for 24 hours. After evaporating the solvent and the excess allyl bromide, 150 ml of water was added to the residue. The suspended mixture was extracted twice with 150 ml portions of dichloromethane. The dichloromethane was evaporated to give a slightly yellow solid (10.4 g). The crude product was recrystallized from methanol to give 7.4 g (62%) of white needles, mp 91-92.5°; ir (potassium bromide): 1710 cm^{-1}; nmr (deuteriochloroform): δ 4.01 (s, 6H), 4.65 (m, 2H), 5.38 (m, 2H), 6.02 (m, 1H), 7.79 (s, 2H).

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22. Found: C, 57.26; H, 5.16.

4-(Tetrahydro-2-pyranoxy)-2,6-pyridinedimethanol (**13**).

The reduction of dimethyl 4-(tetrahydro-2-pyranoxy)-2,6-pyridinedicarboxylate [5] (**10**) was carried out according to the procedure used for

Table V

Positional Paramaters ($\times 10^4$) and Thermal Parameters ($\times 10^3$) for Potassium Thiocyanate Complex of **4** with e.s.d. Values in Parentheses. Hydrogen Atoms of the Polyether Ring Are Omitted

Atom	x	y	z	U	
N1	451(4)	6993(7)	9237(3)	51(2)	[a]
C2	364(5)	7643(8)	9895(4)	53(3)	[a]
C3	1255(5)	8656(9)	10255(5)	70(3)	[a]
O4	2213(3)	7869(5)	10344(3)	55(2)	[a]
C5	3064(6)	8789(9)	10700(4)	72(4)	[a]
C6	4071(6)	7963(10)	10707(5)	70(4)	[a]
O7	4205(3)	7789(6)	9934(3)	62(2)	[a]
C8	5216(5)	7219(10)	9872(5)	71(4)	[a]
C9	5247(6)	6977(10)	9035(5)	71(4)	[a]
O10	4532(4)	5809(6)	8759(3)	60(2)	[a]
C11	4536(6)	5497(9)	7973(4)	70(3)	[a]
C12	3734(6)	4297(8)	7697(4)	69(4)	[a]
O13	2729(4)	4981(5)	7645(3)	59(2)	[a]
C14	1905(5)	3965(8)	7348(4)	69(3)	[a]
C15	891(6)	4761(10)	7331(4)	70(4)	[a]
O16	757(4)	4990(7)	8099(3)	73(2)	[a]
C17	−251(6)	5396(10)	8160(4)	77(4)	[a]
C18	−337(5)	6092(8)	8924(4)	53(3)	[a]
CA3	−505(5)	7492(8)	10250(4)	51(3)	[a]
HA3	−532	7998	10725	61	
CA4	−1338(5)	6586(8)	9900(4)	51(3)	[a]
OA4	−2215(3)	6422(6)	10200(3)	68(2)	[a]
HOA4	−2281	6464	10811(3)	266(59)	
CA5	−1233(5)	5863(8)	9230(4)	53(3)	[a]
HA5	−1778	5206	8978	62	
K	2497(1)	6472(2)	8979(1)	58(1)	[a]
S	2962(2)	9247(3)	7806(1)	84(1)	[a]
C	2653(6)	10413(10)	8428(5)	59(3)	[a]
N	2438(6)	11271(9)	8870(5)	89(4)	[a]

[a] U_{eq} value which is one-third the trace of the orthogonalised U_{ij} tensor.

dimethyl 2,6-pyridinedicarboxylate [15]. A suspension of **10** (15.9 g, 5.38 $\times 10^{-2}$ mole) in 160 ml of ethanol was stirred and cooled in an ice bath. To this suspension was added sodium borohydride (98%, 10.0 g, 0.26 mole) in portions. The mixture was stirred at 0° for 1 hour and then at 25° for 2 hours and refluxed for 14 hours. The solvent was evaporated to give a waxy solid. Acetone (200 ml) was added to the residue and the mixture was refluxed for 1 hour. After the solvent was evaporated, aqueous potassium carbonate solution (60 g in 150 ml of water) was added to the residue and the mixture was refluxed for 2 hours. The solvent was concentrated and 60 ml of saturated brine was added to the residue. The mixture was extracted three times with 150 ml portions of chloroform. The combined layers were dried over anhydrous sodium sulfate and concentrated to give a slightly yellow solid. The crude product was recrystallized from acetone to give a white solid (11.14 g, 87%), mp 115.5-116.5°; nmr (dimethyl sulfoxide-d_6): δ 1.3-2.1 (m, 6H), 3.2-3.9 (m, 2H), 4.48 (d, J = 6.5 Hz, 4H), 5.36 (t, J = 6.5 Hz, 2H), 5.62 (s, 1H), 6.96 (s, 2H).

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16. Found: C, 60.14; H, 7.12.

4-Octoxy-2,6-pyridinedimethanol (**14**).

Dimethyl 4-octoxy-2,6-pyridinedicarboxylate [16] was reduced as above to give compound **14** (91%), mp 80-81°; nmr (deuteriochloroform): δ 0.89 (t, 3H), 1.32 (m, 10H), 1.76 (t, 2H), 4.00 (t, 2H), 4.0 (broad, 2H, OH), 4.64 (s, 4H), 6.70 (s, 2H).

Anal. Calcd. for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43. Found: C, 67.43; H, 9.40.

4-Allyloxy-2,6-pyridinedimethanol (**15**).

Compound **12** was reduced as above to give **15** (76%), mp 121-122°; nmr (dimethyl sulfoxide-d_6 + dideuterium oxide): δ 4.48 (s, 4H), 4.64 (m, 2H), 5.16-5.52 (m, 2H), 5.80-6.28 (m, 1H), 6.88 (s, 2H).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71. Found: C, 61.60; H, 6.81.

4-*n*-Octyl-3,6,9-trioxaundecane-1,11-ditosylate (**16**) (see Figure 2B).

To a stirred solution of 1.8 g (8×10^{-2} mole) of sodium and 448 g (7.2 mole) of ethylene glycol under nitrogen at 130° was added 104.6 g (0.66 mole) of 1,2-epoxydecane over a 1-hour period. This mixture was stirred at 150° for 2 days and the excess ethylene glycol was distilled under vacuum. The resulting residue was mixed thoroughly in a mixture of 300 ml of ice cold 6% sulfuric acid and 600 ml of methylene chloride. The phases were separated and the organic phase was washed successively with 300 ml portions of saturated brine, saturated aqueous sodium bicarbonate and again with saturated brine. The organic phase was dried over anhydrous magnesium sulfate and distilled to give 132 g (92%) of 3-oxatridecane-1,5-diol as a waxy solid, bp 128-132°/0.05 mm; ir (neat) 3400 cm^{-1}; nmr (deuteriochloroform): δ 0.87 (t, 3H), 1.24 (m, 14H), 3.08-3.92 (m, 7H), 4.0 and 4.2 (broad, 2H).

The diol (37.3 g, 0.17 mole) in 120 ml of *t*-butyl alcohol was added to a stirred solution of 32.5 g (0.83 mole) of potassium in 1 l of *t*-butyl alcohol under nitrogen. Chloroacetic acid (36.4 g, 0.39 mole) in 120 ml of *t*-butyl alcohol was added over a 1-hour period to the above solution at reflux temperature. The resulting mixture was stirred at reflux temperature for 3 days. The *t*-butyl alcohol was distilled under vacuum and the residue was mixed with 700 ml of water. The aqueous phase was washed twice with 300 ml portions of ethyl acetate. The *p*H of the aqueous phase was adjusted to 2.0 with hydrochloric acid in an ice bath, and the aqueous phase was saturated with sodium chloride. The aqueous phase was then extracted once with 400 ml and twice with 200 ml portions of ethyl acetate. The combined (total 800 ml) organic extracts were washed twice with 300 ml of saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed and the residue (50.3 g, 88%) was dissolved in methanol. Thionyl chloride (100 ml, 1.38 mole) was slowly added to the methanol solution at 0°. The resulting mixture was stirred at 0° for 1 hour and at reflux temperature for 14 hours. The solvent was then removed and the residue dissolved in 600 ml of ethyl acetate. The organic phase was washed with 300 ml of saturated brine, 300 ml of saturated aqueous sodium bicarbonate and again with 300 ml of saturated brine. The material was dried over anhydrous magnesium sulfate and distilled to give 49 g (90%) of dimethyl 4-octyl-3,6,9-trioxa-1,11-undecanedicarboxylate, bp 145-148°/0.05 mm; ir (neat): 1750, 1725 cm^{-1}; nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.28 (m, 12H), 1.5 (m, 2H), 3.54-3.82 (m, 11H), 4.16 (s, 3H), 4.26 (s, 3H).

The dimethyl ester (26.9 g, 0.074 mole) dissolved in 200 ml of dry ether was slowly added to a stirred suspension of 6.6 g (0.17 mole) of lithium aluminum hydride in 300 ml of dry ether at 0° under nitrogen. This mixture was stirred under reflux for 4 days. The mixture was cooled to 0°, and 10 ml of saturated aqueous ammonium chloride and 20 ml of 10% aqueous sodium hydroxide were slowly added consecutively. The resulting mixture was stirred for 1 day and filtered. The residue was washed with four 100 ml portions of ether. The combined ether extracts were washed with 100 ml of cold saturated brine, and this aqueous layer was washed with ether. The combined ether layers were distilled to give 21.6 g (93%) of 4-*n*-octyl-3,6,9-trioxaundecane-1,11-diol, bp 156-158°/0.05 mm; ir (neat): 3420 cm^{-1}; nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.10-1.76 (m, 14H), 3.3-4.0 (m, 15H), 4.20 (broad, 2H).

The 4-octyl-substituted diol (19.1 g, 0.62 mole) in 40 ml of pyridine was reacted with 26.6 g (0.14 mole) of tosyl chloride in 80 ml of pyridine at 0°. The mixture was stirred at 0° for 8 hours and at room temperature for 12 hours. The reaction mixture was poured onto 200 ml of ice and water and the water was extracted with two 150 ml portions of methylene chloride. The combined organic layers were washed twice with 100 ml portions of 6 *N* hydrochloric acid and once with 100 ml of 5% aqueous brine. Most of the solvent was removed and 100 ml of ether was added. The organic material was dried over anhydrous sodium sulfate and the solvents were removed to give a viscous oil. The product was passed through an alumina column using methylene chloride to give **16**, 25.3 g (66%) of a slightly yellow oil; nmr (deuteriochloroform): δ 0.88 (t, 3H),

2.25 (s, 14H), 2.44 (s, 6H), 3.20-3.84 (m, 11H), 4.00-4.24 (m, 4H), 7.32 (d, 4H), 7.75 (d, 4H). A carbon-hydrogen analysis for macrocycle **6** prepared from **16** was satisfactory, so **16** was not further analyzed.

4-(Tetrahydro-2-pyranoxy)-2,6-pyridinedimethylditosylate (**17**) (Figure 2C).

The procedure of Mitra and coworkers [17] for the preparation of 2-pyridinemethyltosylate was used to prepare **17**. A mixture of compound **13** (4.78 g, 0.02 mole), 2.0 (0.05 mole) of sodium hydride (60% in mineral oil) and 180 ml of purified anhydrous tetrahydrofuran (THF) was stirred at room temperature under nitrogen for 10 minutes and then refluxed for 30 minutes. The mixture was cooled to −75° (dry ice-acetone bath) and stirred while 8.58 g (0.045 mole) of tosyl chloride in 40 ml of anhydrous THF were added over a 20-minute period. The resulting mixture was stirred an additional hour at −75° and then allowed to warm to room temperature for 30 minutes. The solvent was removed under vacuum (30°) and a mixture of 100 ml of cold saturated aqueous sodium bicarbonate and 200 ml of methylene chloride were added. The resulting mixture was thoroughly mixed in a separatory funnel. The aqueous layer was separated and the organic layer was washed once with 100 ml of saturated brine. After drying over anhydrous magnesium sulfate, the solvent was removed and the resulting oil was recrystallized from ether to give 6.0 g (55%) of compound **17**, mp 89-91°; nmr: (δ) 1.5-2.0 (m, 6H), 2.42 (s, 6H), 3.62 (m, 2H), 5.00 (s, 4H), 5.44 (m, 1H), 6.98 (s, 2H), 7.16 (d, 4H), 7.80 (d, 4H).

Anal. Calcd. for $C_{26}H_{29}NO_8S_2$: C, 57.02; H, 5.34; S, 11.71. Found: C, 56.98; H, 5.43; S, 11.61.

General Procedure for the Synthesis of New Macrocyclic Compounds From the Appropriate 4-Substituted-2,6-Pyridinedimethanol (**13**, **14**, or **15**).

An excess of potassium metal (sodium for compound **3**) was dissolved in *t*-butyl alcohol. The pyridinedimethanol starting material (**13**, **14**, or **15**) was added to the *t*-butyl alcohol solution. An equal amount of the ditosylate derivative of the appropriate oligoethylglycol in dioxane was added over a 1-hour period to the stirring solution at room temperature. The resulting mixture was stirred under reflux for 24 hours and then cooled and filtered to remove the solid potassium tosylate. The solid residue was washed with methylene chloride. The combined filtrate and methylene chloride wash was evaporated to give in most cases a viscous brown oil. For the synthesis of compounds **3-7**, the crude product was refluxed for 24 hours in methanol containing a small amount of *p*-toluenesulfonic acid (10 mole % of starting material). The resulting mixture was cooled and neutralized with solid potassium hydroxide. The solvent was removed and the residue was passed through an alumina column using methylene chloride or methylene chloride mixed with either methanol or ethyl acetate as eluents. Specific details are given for each new compound.

3,6,9,12-Tetraoxa-18-azabicyclo[12.3.1]octadeca-14,17-diene-16(18-*H*)-one (**3**).

Sodium metal (1.35 g, 5.87 × 10^{-2} mole), 300 ml of *t*-butyl alcohol, 6.38 g (2.67 × 10^{-1} mole) of the ditosylate of triethylene glycol (mp 78.5-79.5) [18] in 100 ml of dioxane were used. The product was recrystallized from acetone to give **3** as white needles, 1.02 g (14%), mp 150-151°; ir (potassium bromide): 3250, 3300, 1640 cm^{-1}; nmr (deuteriochloroform): δ 3.70 (s, 4H), 3.73 (s, 8H), 4.51 (s, 4H), 6.16 (s, 2H), 9.60 (s, 1H).

Anal. Calcd. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11. Found: C, 58.08; H, 7.07.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1] heneicosa-17,20-diene-19-(21-*H*)-one (**4**) From Compound **13**.

Potassium metal (7.2 g, 0.184 mole), 1 l of *t*-butyl alcohol, 19.8 g (8.3 × 10^{-2} mole) of **13** and 41.6 g (8.3 × 10^{-2} mole) of the ditosylate of tetraethylene glycol (oil) in 250 ml of dioxane were used. The product was recrystallized from acetone to give white crystals as the monohydrate, 7.24 g (26%), mp 104-105°; ir (potassium bromide): 3250, 3350, 3450, 1640 cm^{-1}; nmr (deuteriochloroform + dideuterium oxide): δ 3.64 (s, 8H), 3.72 (s, 8H), 4.36 (s, 4H), 6.20 (s, 2H).

Anal. Calcd. for $C_{15}H_{23}NO_6 \cdot H_2O$: C, 54.37; H, 7.60. Found: C, 54.49; H, 7.70.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19-(21-*H*)-one **4** from Compound **17**.

A mixture of 0.97 g (5 × 10^{-3} mole) of tetraethylene glycol, 0.6 g (1.5 × 10^{-2} mole) of sodium hydride (60% in mineral oil) and 150 ml of anhydrous THF was stirred at room temperature under nitrogen for 10 minutes and refluxed for 30 minutes. To this solution at -75° was added 2.74 g (5 × 10^{-3} mole) of compound **17** in 150 ml of anhydrous THP over a period of 40 minutes. The resulting mixture was stirred at −75° for 1 hour and at room temperature for 3 days. The solvent was removed and 50 ml of cold saturated aqueous sodium bicarbonate and 100 ml of methylene chloride were added. This mixture was thoroughly mixed and the aqueous phase was adjusted to *p*H 7.0 with acetic acid. The mixture was again mixed thoroughly and separated. The aqueous phase was extracted with two 50 ml portions of methylene chloride. The combined methylene chloride layers were dried and the solvent was removed under vacuum. The crude product (2.03 g) was dissolved in 90 ml of methanol along with 0.3 g of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed for 24 hours. The solvent was removed and the crude product was dissolved in 80 ml of methylene chloride. The methylene chloride solution was washed with 50 ml of aqueous sodium bicarbonate. The aqueous phase was adjusted to *p*H 8.0 with acetic acid and it was washed twice with 30 ml portions of methylene chloride. The combined methylene chloride layers were dried over anhydrous magnesium sulfate and the solvent was removed. The solid residue was recrystallized from acetone to give 0.45 g (27%) of compound **4**, which had the same physical properties as that reported above.

3,6,9,12,15,18-Hexaoxa-24-azabicyclo[18.3.1]tetracosa-20,23-diene-22-(24-*H*)-one (**5**).

Potassium metal (3.08 g, 7.9 × 10^{-2} mole), 500 ml of *t*-butyl alcohol, 8.6 g (3.6 × 10^{-2} mole) of **13** and 19.6 g (3.6 × 10^{-2} mole) of the ditosylate of pentaethylene glycol (oil) in 150 ml of dioxane were used. The product was isolated as the potassium thiocyanate complex, 3.7 g (23%), mp 144.5-146°.

Anal. Calcd. for $C_{18}H_{27}H_2O_7SK$: C, 47.56; H, 5.99. Found: C, 47.32; H, 6.05.

The complex was passed through an alumina column using chloroform-methanol (9:1) as the eluent to give compound **5** as a viscous oil; ir (neat): 1640 cm^{-1}; nmr (deuteriochloroform + dideuterium oxide): δ 3.70 (s, 12H), 3.72 (s, 8H), 4.45 (s, 4H), 6.27 (s, 2H).

7-*n*-Octyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19(21-*H*)-one (**6**).

Potassium metal (2.7 g, 6.9 × 10^{-2} mole), 400 ml of *t*-butyl alcohol, 7.6 g (3.1 × 10^{-2} mole) of **13** and 19.2 g (3.1 × 10^{-2} mole) of ditosylate **16** in 100 ml of dioxane were used. The viscous oil product was recrystallized from ether to give 5.3 g (38%) of a white solid monohydrate, mp 41.5-43°; ir (potassium bromide): 1640 cm^{-1}; nmr (deuteriochloroform + dideuterium oxide): δ 0.88 (t, 3H), 1.26 (s, 12H), 1.56 (m, 2H), 3.2-3.9 (m, 15H), 4.2-4.6 (m, 4H), 6.20 (s, 2H).

Anal. Calcd. for $C_{23}H_{39}NO_6 \cdot H_2O$: C, 62.28; H, 9.32; mol wt, 443.59. Found: C, 62.12; H, 9.17; mol wt, 423.1.

3,6,12,15-Tetraoxa-9-thia-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19-(21-*H*)-one (**7**).

Potassium metal (6.9 g, 0.18 mole), 1 l of *t*-butyl alcohol, 19.1 g (8 × 10^{-2} mole) of **13** and 41.4 g (8 × 10^{-2} mole) of the ditosylate of 3,9-dioxa-6-thiaundecane-1,11-diol (oil) in 200 ml of dioxane were used. The light yellow crude solid was recrystallized from ethyl acetate to give white crystals, 2.78 g (11%), mp 63-64°; ir (potassium bromide): 1640 cm^{-1}; nmr (deuteriochloroform): δ 2.87 (t, J = 5.8 Hz, 4H), 3.71 (s, 8H), 3.78 (t, J = 5.8 Hz, 4H), 4.50 (s, 4H), 6.21 (s, 2H), 9.5 (s, 1H).

Anal. Calcd. for $C_{15}H_{23}NO_5S$: C, 54.69; H, 7.04; mol wt, 329.42. Found: C, 54.73: H. 7.17; mol wt, 356.4.

19-*n*-Octoxy-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**8**) From Compound **14**.

Potassium metal (4.4 g, 0.11 mole), 700 ml of *t*-butyl alcohol, 13.7 g (5.1 $\times 10^{-2}$ mole) of **14** and 25.8 g (5.1 $\times 10^{-2}$ mole) of the ditosylate of tetraethylene glycol were used. The crude product was not refluxed in methanol and *p*-toluene solfonic acid but was recrystallized from acetone to give 14.5 g (45%) of the potassium tosylate complex of **8** as a white solid, mp 126.5-127.5°; nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.30 (s, 10H), 1.76 (m, 2H), 2.28 (s, 3H), 3.40-3.84 (m, 16H), 3.96 (s, 2H), 4.52 (s, 4H), 6.56 (s, 2H), 7.00 (d, J = 7.9 Hz, 2H), 7.75 (d, J = 7.9 Hz, 2H).

Anal. Calcd. for $C_{30}H_{46}NO_9SK$: C, 56.67; H, 7.29. Found: C, 56.71; H, 7.32.

The complex was passed through an alumina column with ethyl acetate as eluent to give free ligand **8** as a slightly yellow oil; nmr (deuteriochloroform): δ 0.89 (t, 3H), 1.32 (s, 10H), 1.77 (m, 2H), 3.61 (s, 8H), 3.77 (s, 8H), 4.00 (t, 2H), 4.67 (s, 4H), 6.75 (s, 2H).

Anal. Calcd. for $C_{23}H_{39}NO_6$: C, 64.91; H, 9.24; mol wt, 425.57. Found: C, 64.77; H, 9.32; mol wt. 431.6.

19-*n*-Octoxy-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**8**) from Compound **4** and *n*-Octyl Bromide.

To a solution of 0.2 g (5.6 $\times 10^{-3}$ mole) of potassium metal, 50 ml of *t*-butyl alcohol and 1.6 g (4.8 $\times 10^{-3}$ mole) of **4** was added 1.1 g (5.6 $\times 10^{-3}$ mole) of *n*-octyl bromide. The resulting mixture was refluxed for 2 days. The solvent was removed to give white hygroscopic crystals which were believed to be the potassium bromide complex of **8**. This solid was passed through an alumina column using ethyl acetate as the eluent to give free ligand 8 as a yellow oil. The oil was further purified on a silica gel column to give 1.54 g (75%) of pure **8** which exhibited the same physical properties as those reported above.

19-Allyloxy-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**9**).

Potassium metal (8.3 g, 0.21 mole), 1 l of *t*-butyl alcohol, 19.5 g (0.1 mole) of **15** and 50.2 g (0.1 mole) of the ditosylate of tetraethylene glycol in 200 ml of dioxane were used. The crude product was not treated with methanol and *p*-toluenesulfonic acid but was recrystallized from acetone-ether to give the potassium tosylate complex of **9**, 23.28 g (41%), mp 139.5-143°; nmr (deuteriochloroform): δ 2.28 (s, 3H), 3.64 (s, 8H), 3.72 (m, 8H), 4.56 (s, 4H), 4.60 (m, 2H), 5.08-5.56 (m, 2H), 5.76-6.28 (m, 1H), 6.60 (s, 2H), 7.04 (d, J = 7.9 Hz, 2H), 7.76 (d, J = 7.9 Hz, 2H).

Anal. Calcd. for $C_{25}H_{34}NO_9SK$: C, 53.27; H, 6.08; mol wt, 563.72. Found: C, 53.16; H, 6.22; mol wt, 570.2.

The complex was passed through an alumina column using ethyl acetate as eluent to give pure **9** as a slightly yellow oil; nmr (deuteriochloroform): δ 3.60 (s, 8H), 3.70 (s, 8H), 4.58-6.48 (m, 2H), 4.61 (s, 4H), 5.20-5.56 (m, 2H), 5.80-6.28 (m, 1H), 6.80 (s, 2H).

The Complex of **4** with Benzylammonium Perchlorate.

Compound **4** (102 mg, 3.08 $\times 10^{-4}$ mole) and benzylammonium perchlorate (64 mg, 3.08 $\times 10^{-4}$ mole) were dissolved in a hot acetone-toluene solution. The solution was cooled to room temperature to give white needles, 61 mg, 38%, mp 189.5-192.0°; ir (potassium bromide): the band at 1640 cm^{-1} was absent; nmr (dimethyl sulfoxide-d_6): δ 3.3 (s, 3H), 3.52 (s, 8H), 3.59 (s, 8H), 4.07 (s, 2H), 4.38 (s, 4H), 6.47 (s, 2H), 7.44 (s, 5H), 8.9 (s, 1H).

Anal. Calcd. for $C_{22}H_{33}ClN_2O_{10}$: C, 50.72; H, 6.38. Found: C, 50.87; H, 6.53.

The Complex of **4** with Potassium Thiocyanate.

Compound **4** (396 mg, 1.20 $\times 10^{-3}$ mole) and potassium thiocyanate (116 mg, 1.20 $\times 10^{-3}$ mole) were dissolved in a hot acetone-toluene solution. The solution was cooled to room temperature to give white needles, 279 mg, 57%, mp 168-168.5°; ir (potassium bromide) no band at 1640 cm^{-1}.

Anal. Calcd. for $C_{16}H_{23}N_2O_6SK$: C, 46.81; H, 5.65. Found: C, 46.81; H, 5.76.

The Complex of **4** with 2-Phenylethylammonium Thiocyanate.

Compound **4** (150.4 mg, 4.54 $\times 10^{-4}$ mole) and 2-phenylethylammonium thiocyanate (81.8 mg, 4.54 $\times 10^{-4}$ mole) were dissolved in a hot acetone-toluene solution. The solution was cooled to room temperature to give white needles, 130 mg, 58%; mp 162-162.5°; ir (potassium bromide): no band at 1640 cm^{-1}; nmr (dimethyl sulfoxide-d_6 + dideuterium oxide): δ 2.6-3.2 (m, 4H), 3.54 (s, 8H), 3.66 (s, 8H), 4.36 (s, 4H), 6.20 (s, 2H), 7.30 (s, 5H).

Anal. Calcd. for $C_{24}H_{35}N_3O_6S$: C, 58.40; H, 7.15. Found: C, 58.32; H, 7.28.

X-ray Determination.

Suitable crystals of **4** and of the potassium thiocyanate complex of **4** were prepared. Lattice parameters for each compound were obtained using a least-squares technique using centered 2θ values measured on the Nicolet R3 automated diffractometer. Single crystal data were obtained using the same instrument. Copper radiation was used for **4** while molydenium radiation was used for the potassium thiocyanate complex of **4**. Intensities were measured using a $\theta - 2\theta$ variable speed scan technique. Crystal data and experimental conditions are summarized in Table III. Trial models for both crystals were obtained using direct methods. After several cycles of refinement, most hydrogen atoms of each structure were located in the difference maps. However, in the refinement process, positions for all hydrogen atoms on the cyclic polyether ring and on the carbons of the pyridine were calculated based on stereochemical considerations. The location of the hydrogen atom on the pyridine nitrogen of **4** and the hydroxy oxygen of the potassium thiocyanate complex of **4** were obtained from the respective difference maps. Positions for both hydrogen atoms of the water of hydration in the crystal structure of **4** were also located in a difference map. Both structures were refined using a cascading least-squares technique. All non-hydrogen atoms in both structures were refined anisotropically. Hydrogen atoms for which positions were calculated were allowed to ride on the neighboring carbon atoms and their isotropic temperature parameters were fixed at 1.2 times Ueq of that atom. The positional parameters and isotropic temperature parameters of NH1, HOW1 and HOW2 of **4** were refined while only the isotropic temperature parameter of HOA4 in the complex was refined. The atomic and thermal parameters of the atoms of **4** and the potassium thiocyanate complex of **4** are contained in Tables IV and V, respectively. The R and Rw values for **4** and for the potassium thiocyanate complex of **4** were 0.045 and 0.069 and 0.067 and 0.076, respectively. All programs used in the data collection and reduction and in the structure solution are part of the Nicoletl R3 system and SHELXTL [19] program package.

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