Proton-Ionizable Crown Compounds. **8**. Synthesis and Structural Studies of Macrocyclic Polyether Ligands Containing a 4-Thiopyridone Subcyclic Unit

Jerald S. Bradshaw*, Peter Huszthy [1], Hiroyuki Koyama [2], Steven G. Wood,

Scott A. Strobel, Richard B. Davidson, Reed M. Izatt*, N. Kent Dalley,

John D. Lamb, and James J. Christensen

Department of Chemistry, Brigham Young University,
Provo, Utah 84602
Received June 3, 1986

Three new proton-ionizable macrocyclic polyether ligands containing the 4-pyridone subcyclic group have been prepared. Two of these ligands contain lipophilic *n*-octyl substituents, the other ligand contains a phenyl substituent. The 15-crown-5 ligand containing both a 4-pyridone subcyclic unit and an *n*-octyl substituent selectively transported lithium cations in a water-methylene chloride-water bulk liquid membrane system. Five crown compounds containing the 4-pyridone subcyclic unit were converted to the 4-thiopyridono-crown compounds when treated with Lawesson's Reagent. The crystal structure of 4-thiopyridono-18-crown-6 shows a carbon-sulfur double bond and a molecule of water hydrogen bonded inside the macrocycle cavity.

Introduction.

We have reported a number of crown compounds each of which contains a proton-ionizable group which is part of the macrocyclic ring (compounds **1-5**, **7** and **8**, Figure 1) [3-8]. Others have studied macrocyclic ligands with one or more pendant arms containing a carboxyl or phenolic group [9-12] or with a phenolic group with the hydroxy function directed into the cavity [13,14]. We are particularly interested in macrocyclic compounds for the transport of cations in liquid membrane systems. Reference [15] gives a review of macrocycle-mediated transport of metal cations in a liquid membrane system. The proton-ionizable macrocyclic ligands allow a proton driven transport where an anion does not accompany the cation [15,16].
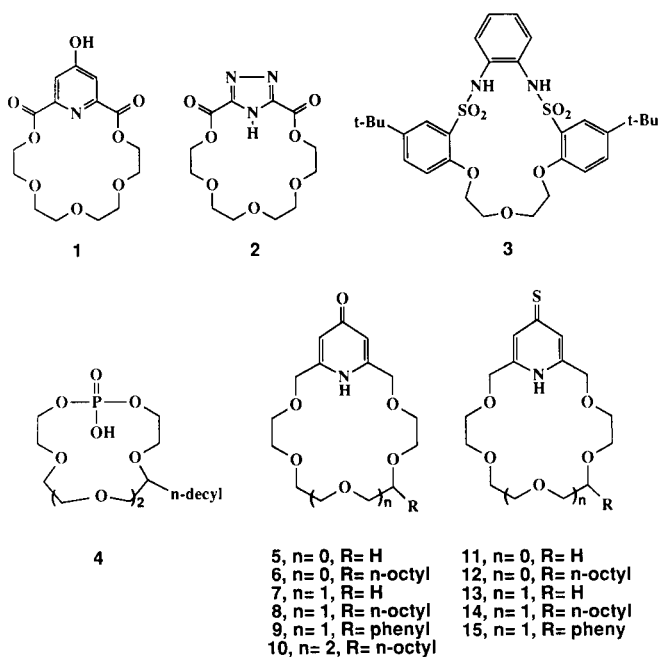
We have observed proton driven transport of cations in a water-methylene chloride-water bulk liquid membrane system employing the crown compounds **3** [7], **4** [8] and **8** [15,16] as the carriers. The 4-pyridone crown **8** has been the most studied. In this case, transport of the alkali metal cations was observed for source phase pH values of 12 and higher. Since the pK_a value for removal of a proton from *n*-octyl substituted **8** is presumably close to that for non-alkyl-substituted **7** (10.98 [17]), transport only occurs when an appreciable amount of the macrocycle is ionized at the source phase-organic phase interface [15].

We want to prepare proton-ionizable macrocyclic ligands with pK_a values which would allow the transport of cations at relatively low source phase pH values. The 4-thiopyridone compounds have been shown to have pK_a values of 8.3 [18]. This paper describes the preparation of 4-pyridono ligands **6**, **9** and **10** which contain lipophilic substituents. The conversion of 4-pyridono ligands **5-9** to the 4-thiopyridono-crown compounds **11-15** as well as a structural study of **13** are also reported in this paper.

Results and Discussion.

Compounds **6**, **9** and **10** were prepared as reported for the other 4-pyridono-crown compounds [5]. Scheme 1 shows the synthesis of **6** by two methods. Either the pyridine dimethanol **16** was reacted with ditosylate **19** or ditosylate **17** was reacted with glycol **18**. The two reactions gave about the same overall yield. We favor the use of polyether tosylate **19** because the heterocyclic tosylate **17** is not easy to prepare [5] and it is a **blistering agent**.

FIGURE I. Structure of Compounds

5, n= 0, R= H
6, n= 0, R= n-octyl
7, n= 1, R= H
8, n= 1, R= n-octyl
9, n= 1, R= phenyl
10, n= 2, R= n-octyl

11, n= 0, R= H
12, n= 0, R= n-octyl
13, n= 1, R= H
14, n= 1, R= n-octyl
15, n= 1, R= pheny

The starting *n*-octyl- and phenyl-substituted glycols used for the preparation of **6, 9** and **10** were prepared from their corresponding epoxides in a manner analogous to the reported preocedure for preparing the *n*-octyl-substituted tetraethylene glycol used to synthesize **8** [5]. Following ring opening of the epoxide moiety with the appropriate reagent, the resulting diol was homologated with chloroacetic acid. The diacid was esterified with methanol and the diester was reduced with lithium aluminum hydride to yield the substituted oligoethylene glycol of desired chain length.

The 4-pyridono-crown compounds were converted to the 4-thiopyridono-crowns by treatment with Lawesson's Reagent [19] (see Scheme 1). The yields for this reaction were not optimized and only **13** and **14** were prepared in reasonable amounts.

SCHEME 1. Preparation of New Crown Compounds 6 and 12
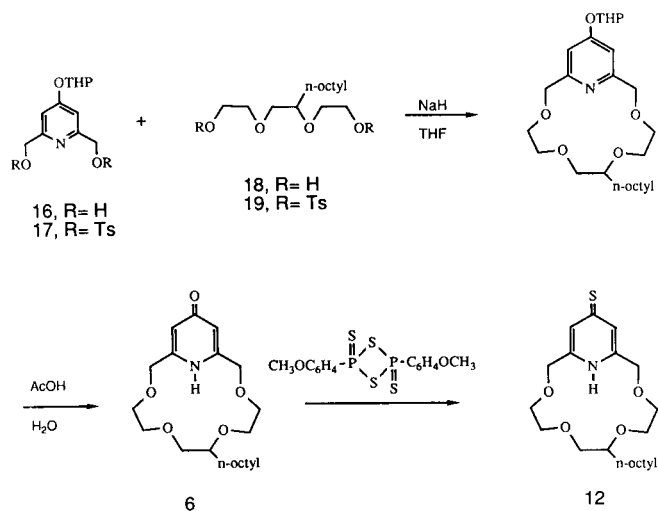
The structures proposed for all new macrocyclic compounds were consistent with data obtained from ir and nmr spectra, combustion analyses and in the case of **13**, a crystal-structure determination. The nmr spectra for the thiono compounds **11-15** exhibited a singlet at δ 7.24 $\pm$ 0.08 for the thiopyridone ring hydrogens while the ring hydrogens for the pyridone compounds **6, 9** and **10** cause signals at δ 6.2 $\pm$ 0.1 [5]. The ^{13}C nmr spectrum for compound **13** had a peak at δ 214.7 indicative of the thiono carbon atom.

The structures shown for **8-10** and **14** and **15** do not show the possible positional isomers. The first step in the preparation of the starting glycols was the reaction of an alkoxide and an epoxide to form a di- or triethylene glycol with a substituent on carbon 1 [5]. Jones and his coworkers [20] showed that the addition of diethylene glycol to pro-

Table I

Positional (x 10^4) and Thermal (Å^2 x 10^3) Parameters for Atoms of **13** with e. s. d. Values in Parenthesis. Hydrogen Atoms Bonded to Carbon Atoms are Omitted.

Atom	x	y	z	Ueq [a]
N1	657(3)	1131(3)	4046(1)	37(1)
HN1	259(27)	1782(34)	3702(11)	68(13)
C2	329(4)	−437(4)	4141(2)	35(1)
C3	−805(3)	−1048(4)	3781(2)	47(2)
O4	−460(2)	−1149(3)	3147(1)	51(1)
C5	−1486(3)	−1722(5)	2769(2)	57(2)
C6	−1105(4)	−1639(5)	2106(2)	60(2)
O7	−1013(3)	2(4)	1925(1)	54(1)
C8	−508(4)	145(5)	1316(2)	57(2)
C9	−492(4)	1873(5)	1132(2)	57(2)
O10	389(2)	2701(3)	1521(1)	48(1)
C11	398(4)	4396(4)	1407(2)	53(2)
C12	1469(4)	5117(5)	1770(2)	49(2)
O13	1225(2)	4987(3)	2419(1)	47(1)
C14	2194(4)	5739(5)	2784(2)	51(2)
C15	1897(4)	5529(4)	3458(2)	46(2)
O16	2012(2)	3856(3)	3617(1)	46(1)
C17	1871(4)	3591(4)	4264(2)	52(2)
C18	1654(2)	1818(5)	4366(2)	39(1)
CA3	1012(3)	−1368(4)	4546(1)	42(1)
CA4	2096(4)	−768(5)	4862(2)	42(2)
SA4	3041(1)	−1940(2)	5318(1)	68(1)
CA5	2357(4)	896(5)	4766(2)	43(2)
OW1	−458(3)	2579(4)	2942(1)	53(1)
HAOW1	163(26)	3278(37)	2748(15)	81(16) [b]
HBOW1	−592(41)	1672(34)	2662(16)	116(20) [b]
OW2	1212(3)	−4726(5)	5921(2)	110(2)
HAOW2	1672(57)	−3929(64)	5667(26)	257(37) [b]

[a] Ueq value is one-third the trace of the orthoganalized Uij tensor.
[b] Value is the isotropic U value.

pylene oxide in the presence of sodium metal gave 5-10% of the isomer with a methyl on carbon number 2. We suspect that in the case of *n*-octyl-substituted compounds **8, 10, 14** and **15**, there would be some 8-*n*-octyl product in addition to the major product as shown. The nmr spectra of the macrocyclic compounds and the starting glycols would be essentially the same for both the 7- and 8-alkyl substituted compounds so the ratio of the two isomers is undeterminable. Compounds **6** and **12** are unique compounds since the 7- and 8-alkyl isomers are the same.

Although the isomers of alkyl-substituted compounds **8** and **10** can not be detected by nmr, the addition product of ethylene glycol and styrene oxide which is the initial reaction product for the preparation of phenyl substituted tetraethylene glycol used to prepare **9**, does show considerable amounts of two isomers. The major product (62%) was found to be 1-phenyl-3-oxapentane-1,5-diol while the minor product (38%) was the 2-phenyl isomer. This assignment is based on the fact that the nmr chemical shifts for benzyl alcohol and the 1-phenyl adduct

Table II

Bond Lengths, Bond Angles and Torsion Angles for **13**

1	2	3	4	1-2 (Å)	1-2-3 (deg)	1-2-3-4 (deg)
C18	N1	C2	C3	1.369(5)	120.9(3)	178.0(3)
N1	C2	C3	O4	1.355(5)	116.4(3)	70.0(4)
C2	C3	O4	C5	1.501(5)	107.7(3)	180.0(3)
C3	O4	C5	C6	1.410(4)	111.5(3)	174.3(3)
O4	C5	C6	O7	1.423(4)	108.7(3)	−69.0(4)
C5	C6	O7	C8	1.480(5)	109.1(3)	173.2(3)
C6	O7	C8	C9	1.411(5)	111.1(3)	177.0(3)
O7	C8	C9	O10	1.419(5)	109.3(3)	66.4(4)
C8	C9	O10	C11	1.478(6)	108.5(3)	−175.7(3)
C9	O10	C11	C12	1.415(4)	112.3(3)	−172.1(3)
O10	C11	C12	O13	1.419(4)	108.1(3)	−67.0(4)
C11	C12	O13	C14	1.486(5)	109.7(3)	−176.9(3)
C12	O13	C14	C15	1.418(4)	111.7(3)	−178.8(3)
O13	C14	C15	O16	1.420(4)	109.0(3)	67.8(4)
C14	C15	O16	C17	1.490(5)	109.0(3)	173.9(3)
C15	O16	C17	C18	1.426(4)	112.0(3)	164.9(3)
O16	C17	C18	N1	1.412(4)	108.2(3)	−55.6(4)
O16	C17	C18	CA5	[a]	[a]	126.6(4)
C17	C18	N1	C2	1.496(5)	116.6(3)	−175.2(3)
C17	C18	CA5	CA4	[a]	123.8(3)	178.2(3)
CA5	C18	N1	C2	1.358(5)	119.6(3)	2.7(5)
C18	CA5	CA4	CA3	[a]	121.9(3)	−4.0(5)
SA4	CA4	CA5	C18	1.690(4)	121.6(3)	175.2(3)
SA4	CA4	CA3	C2	[a]	123.0(3)	−174.4(3)
CA5	CA4	CA3	C2	1.415(6)	115.4(3)	4.9(5)
CA4	CA3	C2	N1	1.408(5)	121.8(3)	−2.1(5)
CA4	CA5	C18	N1	[a]	[a]	0.4(5)
C3	C2	CA3	CA4	[a]	123.4(3)	178.0(3)
CA3	C2	C3	O4	1.357(5)	[a]	−110.1(4)
CA3	C2	N1	C18	[a]	120.2(3)	−1.9(5)
HN1	N1	C2	C3	0.999(26	121.3(16)	−10.0(1.8)
HN1	N1	C2	C3A	[a]	[a]	170.0(1.8)
HN1	N1	C18	C17	[a]	117.3(16)	12.6(1.8)
HN1	N1	C18	C5A	[a]	[a]	−169.5(1.7)
HAOW1	OW1	HBOW1		0.968(30)	106.8(29)	−
HBOW1	OW1	HAOW1		0.968(32)	[a]	−
HAOW2	OW2			0.984(55)	−	−

[a] The value is given previously in the Table.

are similiar as are the shifts for benzyl methyl ether and the 2-phenyl adduct. The nmr peaks for the benzylic hydrogen atoms for macrocycles **9** and **15** are not separated so that the amounts of positional isomers for those compounds are not known.

It is interesting to note that the *n*-octyl-substituted glycols, tosylates and macrocyclic compounds all exhibit a singlet peak in the nmr at about δ 3.4 $\pm$ 0.1 for about 3 hydrogens. This signal is slightly upfield from the normal δ 3.6 of the other protons on carbon atoms adjacent to an ether oxygen. This effect is most apparent for tosylate **19** where the peaks are more separated than with the glycols or ethers. A similar upfield shift for 3 hydrogens was observed for *n*-alkyl-substituted phosphate crown compounds (**4** for example [8]). The reason for the upfield shift is not known. The alkyl substituent destroys the symmetry

of the glycols and crown compounds. Perhaps the long chain alkyl groups cause some aberration of the normal magnetism for the three hydrogens attached to either the carbon bearing the alkyl substituent or the carbon adjacent.

The 4-pyridone structure of **7** was proved by a crystal structure determination [5]. We suspected that **13** would have a 4-thiopyridone structure. A crystal of **13** was prepared under hydrous conditions so that any waters of solvation could also be observed. The crystal structure did reveal two waters of solvation. The conformation of the **13** is shown in Figure 2. The positional and thermal parameters of the atoms are listed in Table I. The atom labels are also included in the figure. The structure revealed one water molecule in the cavity which was hydrogen bonded to the N1, O7 and O13. A similar coordination of water

Table III

Hydrogen Bond Data for **13**

D	H	A	D⋯A (Å)	H⋯A (Å)	D-H⋯A (deg)
N1	HN1	OW1	2.885(4)	1.904(25)	167(2)
OW1	HAOW1	O7	3.094(4)	2.137(32)	169(2)
OW1	HBOW1	O13	2.893(4)	1.935(30)	170(3)
OW2	HAOW2	SA4	3.270(4)	2.311(56)	165(5)

was found in **2**, the triazolo derivative [3]. The conformation of the molecule was similar to other complexed crown compounds. The torsion angles have low energy values and the heteroatoms form a nearly regular hexagon (Figure 2). The bond lengths and angles and torsion angles
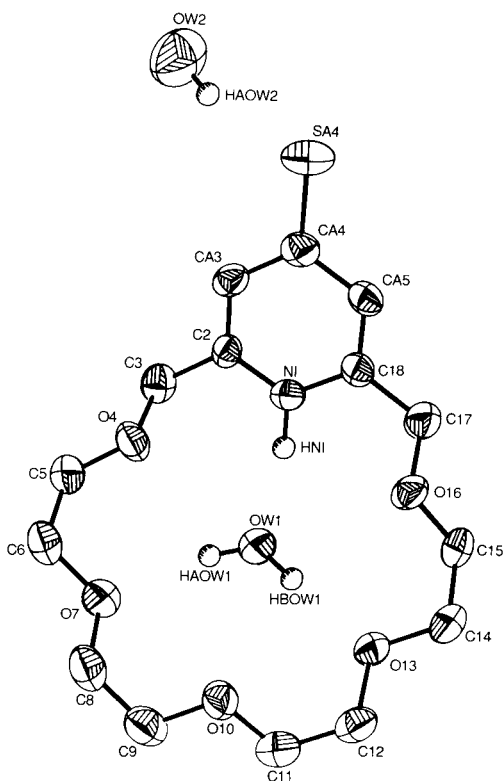
Figure 2. Conformation of the dihydrate of **13** with H atoms bonded to ring carbon atoms omitted for clarity.

are listed in Table II. The structure was clearly that for a 4-thiopyridone which is in agreement with ^{13}C nmr data. The bond lengths (Table II) show two double bonds in the six membered ring as well as a C-S double bond. The hydrogen atom on N1 was clearly evident from a difference map. Data for the three hydrogen bonds which interact with the water molecule are listed in Table III. A second water molecule is located outside the cavity and is hydrogen bonded to the sulfur atom.

Compounds **6** and **14** were tested as cation carriers through a water-methylene chloride-water bulk liquid membrane system using techniques that have been described [16,21]. Preliminary data for the transport of cations by compound **6** show that it is selective for lithium ions. Compound **14** was found to be an effective carrier for all the alkali metal cations. More details on the transport of cations by compounds **6** and **14** will be published when the work is finished.

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

Table IV

Crystal and Experimental Data for **13**

formula	$C_{15}H_{23}NO_5S \cdot 2H_2O$
formula weight	365.4
F(000)	784
crystal size (mm)	0.45 x 0.30 x 0.02
space group	P2$_1$/n
a(Å)	10.511(4)
b(Å)	8.247(3)
c(Å)	21.408(10)
β (deg)	90.59(4)
V (Å^3)	1856(1)
Z	4
D$_x$(gcc^{-1})	1.31
μ (cm^{-1})	1.99
sin θ/λ	0.59
total data	3860
unique obs data	1830
R	0.070
Rw	0.033
Δ map max (e Å^{-3})	0.32
Δ map min (e Å^{-3})	−0.29
max shift/e. s. d.	0.004

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 were prepared by the reaction of the corresponding oligoethylene glycols with *p*-toluenesulfonyl chloride in pyridine [22] (see below for **19**). All other starting materials were prepared according to the following procedures.

4-*n*-Octyl-3,6-dioxa-1,8-octanediol (**18**).

1,2-Epoxydecane (78.14 g, 0.5 mole) was added dropwise to a stirring solution of 52 ml (1.22 moles) of 90% aqueous formic acid. This mixture was stirred overnight at room temperature. The reaction mixture was cooled to about 5° and a solution of 50 g (1.25 moles) of sodium hydroxide in 300 ml of water was added dropwise. The resulting mixture was extracted three times with 200 ml portions of methylene chloride. The combined methylene chloride extracts were dried over anhydrous magnesium sulfate. The solvent was evaporated and the *n*-octylethylene glycol was distilled to give 58.8 g (68%) as a waxy solid, bp 110-130°/0.025 mm. This glycol was reacted first with chloroacetic acid followed by treatment with thionyl chloride and methanol to form dimethyl 4-*n*-octyl-3,6-dioxaoctanedioate in a like manner as reported for the preparation of dimethyl 4-*n*-octyl-3,6,9,12-tetraoxatetradecanedioate [8]. This product was distilled to give an oil, 78%, bp 128-132°/0.05 mm; ir (neat): 1750 cm^{-1}; nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.08-1.12 (m, 14H), 3.52 (s, 2H), 3.76 (m, 5H), 4.13 (s, 3H), 4.28 (s, 3H). This diester was reduced with lithium aluminum hydride to form **18** as reported for the preparation of 4-*n*-octyl-3,6,9,12-tetraoxa-1,14-tetradecanediol [5]. Product **18** was purified by distillation, 85%; ir (neat): 3400 cm^{-1} (broad); nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.04-1.68 (m, 14H), 3.52 (s, 3H), 3.76 (m, 4H), 4.82 (broad, 2H, signal disappeared in dideuterium oxide). Compound **6**, a derivative of **18**, gave a satisfactory elemental analysis.

4-*n*-Octyl-3,6-dioxaoctane-1,8-ditosylate (**19**).

To an ice cold stirring solution of 17.8 g (0.068 mole) of diol **18** in 58 ml of anhydrous pyridine was added dropwise, 29.0 g (0.152 mole) of *p*-toluenesulfonyl chloride in 112 ml of pyridine. The mixture was stirred at 0° for 6 hours and then at 14° for 24 hours. The reaction mixture was poured onto 900 g of ice and extracted three times with 150 ml portions of methylene chloride. The combined methylene chloride extracts were washed successively with two portions of 140 ml of 6 *N* aqueous hydrochloric acid and once with 100 ml of saturated brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate/hexane (1:4) as the eluant to give 26.0 g (67%) of **19** as a viscous oil; nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.02-1.52 (m, 14H), 2.43 (s, 6H), 3.36 (s, 3H), 3.68 (m, 4H), 4.12 (m, 4H), 7.33 (d, 4H), 7.78 (d, 4H). Compound **6**, a derivative of **19**, gave a satisfactory elemental analysis.

4-Phenyl-3,6,9-trioxaundecane-1,11-diol (**20**).

Styrene oxide (78.8 g, 0.66 mole) was reacted with an excess of ethylene glycol and base to form 82 g (69%) of a mixture of 1- and 2-phenyl-3-oxa-1,5-pentanediol by the same procedure that was used to prepare 1-*n*-octyl-3,6-dioxa-1,8-octanediol from 1,2-epoxydecane and diethylene glycol [8]. The product was an oil, bp 125-127°/0.05 mm (lit [23] 156-157°/3 mm); ir (neat): 3400, 750, 690 cm^{-1}; nmr (deuteriochloroform): δ 3.52 (m, 6H), 4.44 (dd, 0.38H), 4.68 (broad, 2H, peak disappeared in dideuterium oxide), 4.90 (dd, 0.62H), 7.23 (m, 5H). This phenyl-substituted glycol (25.9 g, 0.14 mole) was used without further purification for the preparation of dimethyl 4-phenyl-3,6,9-trioxaundecanedioate from 30.3 g (0.32 mole) of chloroacetic acid by the same procedure that was used to prepare dimethyl 4-*n*-octyl-3,6-9,12-tetraoxatetradecanedioate from the appropriate glycol and chloroacetic acid [8]. The product was an oil, 37 g (80%), bp 160°/0.05 mm; ir (neat): 1735 cm^{-1}; nmr (deuteriochloroform): δ 3.70 (m, 8H), 4.12 (m, 4H), 4.62 (m, 1H), 7.32 (s, 5H). Dimethyl 4-phenyl-3,6,9-trioxaundecanedioate (24.07 g, 0.074 mole) was reduced by lithium aluminum hydride to form compound **20** by the same

procedure that was used to prepare 4-*n*-octyl-3,6,9,12-tetraoxa-1,14-tetradecanediol [5]. Compound **20** was an oil, 15.9 g (80%); ir (neat): 3400 cm^{-1}; nmr (deuteriochloroform): δ 3.68 (m, 14H), 4.18 (broad, 2H, peak disappeared in dideuterium oxide), 4.62 (m, 1H), 7.36 (s, 5H). Compound **9**, a derivative of **20**, gave a satisfactory elemental analysis.

General Procedure for the Synthesis of New Macrocyclic Compounds Containing the 4-Pyridone Subcyclic Unit **6, 9** and **10** from **17** (see Scheme I).

The appropriate diol (7.3 mmoles) in 100 ml of purified anhydrous tetrahydrofuran (THF) was slowly added to a stirring suspension of 0.88 g (22 mmoles, 60% in mineral oil) of sodium hydride in 150 ml of purified THF under nitrogen and at $-75°$. The mixture was stirred at $-75°$ for 30 minutes. To this mixture at $-75°$ was added dropwise, 4.0 g (7.3 mmoles) of **17** [5] (see Scheme I) in 250 ml of purified THF. The resulting mixture was stirred at $-75°$ for 30 minutes followed by stirring at room temperature for 20 hours. Acetic acid (2.1 g, 35 mmoles) was added to the reaction mixture and the solvents were evaporated under reduced pressure. The residue was dissolved in 300 ml of methylene chloride. The organic phase was washed with 100 ml of aqueous sodium bicarbonate. The aqueous phase was washed with 100 ml of methylene chloride. The combined methylene chloride layers were dried over anhydrous magnesium sulfate and the solvent was removed. The residue was stirred under reflux in 50 ml of acetic acid and 10 ml of water for 3 hours. The solvents were removed under reduced pressure and 40 ml of toluene was added and removed under reduced pressure to remove all traces of water. The product was purified as indicated below.

7-*n*-Octyl-3,6,9,12-tetraoxa-18-azabicyclo[12.3.1]octadeca-14,17-diene-16(18*H*)-one (**6**) (see Scheme I).

Compound **6** was purified by chromatography on silica gel using ethanol/toluene (1:6) as eluant to give 2.0 g (52%) of a waxy solid; ir (neat): 3340, 1640 cm^{-1}; nmr (deuteriochloroform): δ 0.87 (t, 3H), 1.02-1.8 (m, 14H), 3.46 (s, $\approx$ 3H), 3.66 (m, 8H), 4.48 (s, 4H), 6.15 (s, 2H), 9.75 (broad, 1H, signal disappeared in dideuterium oxide).

Anal. Calcd. for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25; mol. wt., 381.4. Found: C, 66.34; H, 9.23; mol. wt., 404.

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

Compound **9** was purified by chromatography on silica gel using ethanol/dichloromethane (1:6) as eluant to give 0.85 g (29%) of a viscous oil. It was crystallized from acetone to give **9**, mp 90.5-93°; ir (potassium bromide): 3525, 3470, 3385, 3290, 1635, 770, 700 cm^{-1}; nmr (deuteriochloroform): δ 3.36-3.80 (m, 16H), 4.32-4.44 (m, 4H), 4.52-4.68 (m, 1H), 6.24 (s, 2H), 7.37 (s, 5H), 11.40 (broad, 1H, signal disappeared in dideuterium oxide).

Anal. Calcd. for $C_{21}H_{27}NO_6\cdot\tfrac{3}{4}H_2O$: C, 62.59; H, 7.13, mol. wt., 407.5. Found: C, 62.50; H, 7.22; mol. wt., 455.

7-*n*-Octyl-3,6,9,12,15,18-hexaoxa-24-azabicyclo[18.3.1]tetracosa-20,23-diene-22(24-*H*)-one (**10**).

Compound **10** was purified by chromatography on silica gel using ethanol/toluene (1:5) as eluant to give 0.97 g (28%) of a viscous oil; ir (neat): 3500, 3340, 3240, 1635 cm^{-1}; nmr (deuteriochloroform): δ 0.87 (t, 3H), 1.06-1.55 (m, 14H), 3.50 (s, $\approx$ 3H), 3.68 (m, 16H), 4.47 (s, 4H), 6.27 (s, 2H), 10.7 (broad, 1H, signal disappeared in dideutrium oxide).

Anal. Calcd. for $C_{25}H_{43}NO_7$: C, 63.94; H, 9.23. Found: C, 64.08; H, 9.18.

Preparation of **6** from **16** (see Scheme I).

Compound **16** (4.79 g, 20 mmoles) [5] in 350 ml of THF was added dropwise to a stirring suspension of 1.12 g (28 mmoles) of sodium hydride (60% in mineral oil) and 50 ml of purified THF at room temperature under nitrogen. The mixture was stirred for 10 minutes at room temperature and then refluxed for 2 hours under nitrogen. The mixture was cooled to $-75°$ and 11.4 g (20 mmoles) of **19** in 300 ml of THF was added to the stirring mixture over a 1.5 hour period under

nitrogen. The resulting reaction mixture was stirred at −75° for an additional 10 minutes and then refluxed for 6 days. The mixture was cooled and reacted with 30 g of ice. The solvents were removed under vacuum. The residue was shaken in a mixture of 50 ml of saturated aqueous sodium bicarbonate and 300 ml of methylene chloride. The aqueous layer was washed with 50 ml of methylene chloride. The combined methylene chloride phases were dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. The residue was stirred under reflux in a mixture of 100 ml of acetic acid and 20 ml of water for 4 hours. The solvent was evaporated under vacuum and the residue was shaken in a mixture of 250 ml of methylene chloride and 100 ml of saturated aqueous sodium bicarbonate. The aqueous layer was acidified to pH 7 with acetic acid. The two layers were again mixed and the phases were separated. The aqueous phase was washed with 100 ml of methylene chloride. The combined methylene chloride layers were dried over anhydrous magnesium sulfate and the solvent was evaporated under vacuum. The oily residue was purified by silica gel chromatography to give 3.8 g (50%) of **6** which had the same physical and spectral properties as reported above for **6** prepared from **17**.

General Procedure to Prepare the 4-Thiopyridono-Crowns 11-15 from 5-9.

The 4-pyridono-crowns (about 2.2 mmoles) were refluxed with 2.2 mmoles of Lawesson's Reagent (Aldrich 22,743-9) in 10 ml of anhydrous toluene for 20 hours under nitrogen. The solvent was evaporated and the residue was purified as described below.

3,6,9,12-Tetraoxa-18-azabicyclo[12.3.1]octadeca-14,17-diene-16(18-*H*)-thione (11).

The crude product was dissolved in 10 ml of methylene chloride. Silica gel (2 g) was added to this solution and the solvent was evaporated. The resulting silica gel was put on top of a freshly prepared silica gel column and the product was eluted with toluene then toluene/ethanol (10:1) and then toluene/ethanol (6:1). The product was recrystallized from acetone to give 0.26 g (46%) of **11**, mp 153-155°; nmr (deuteriochloroform): δ 3.68 (m, 12H), 4.53 (s, 4H), 7.24 (s, 2H), 10.35 (broad, 1H, signal disappeared in dideuterium oxide).

Anal. Calcd. for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; S, 11.24. Found: C, 54.73; H, 6.68; S, 11.04.

7-*n*-Octyl-3,6,9,12-tetraoxa-18-azabicyclo[12.3.1]octadeca-14,17-diene-16(18-*H*)-thione (12).

The crude product was purified by silica gel column chromatography using toluene/hexane (1:1), toluene and toluene/ethanol (25:1) as eluants. The product was further purified by preparative silica gel thick layer chromatography using ethanol/chloroform (1:15) as eluant to give 59 mg (8%) of **12** as a waxy solid. It was further purified by preparative silica gel thick layer chromatography using ethanol/toluene (1:3) as eluant to give orange-yellow crystals, mp 82-85°; ir (potassium bromide): 3340, 1620 cm⁻¹; nmr (deuteriochloroform): δ 0.91 (t, 3H), 1.04-1.65 (m, 14H), 3.50 (s, ≈ 3H), 3.68 (m, 8H), 4.52 (s, 4H), 7.23 (s, 2H), 10.40 (broad, 1H, signal disappeared in dideuterium oxide).

Anal. Calcd. for $C_{21}H_{35}NO_4S$: C, 63.44; H, 8.87. Found: C, 63.51; H, 8.76.

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

The crude product was titurated with a small amount of acetone. The precipitate (0.41 g, 62% from 0.63 g of **7** [5]) was recrystallized from dimethylformamide and acetone (mp 176-178°) and then water, mp 182-183°; ¹H nmr (deuteriochloroform): δ 3.58 (2s, 16H), 4.32 (s, 4H), 7.22 (s, 2H), 7.22 (broad, 1H, signal disappeared in dideuterium oxide); ¹³C nmr (deuteriochloroform): δ 68.74, 70.15, 70.32, 70.43, 127.60, 141.98, 214.7 (C=S).

Anal. Calcd. for $C_{15}H_{23}NO_5S$: C, 54.69; H, 7.04; S, 9.73. Found: C,

54.80; H, 7.04; S, 9.76.

7-*n*-Octyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-diene-19(21-*H*)-thione (14).

The crude product was chromatographed on silica gel using toluene/-hexane (1:1), toluene, and ethanol/toluene (1:20) to give 0.35 g (40% from **8** [5]), mp 118-120° (methanol); nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.02-1.56 (m, 14H), 3.48 (s, ≈ 3H), 3.66 (m, 14H), 4.46 (m, 4H), 7.28 (s, 2H), 11.12 (broad, 1H).

Anal. Calcd. for $C_{23}H_{39}NO_5S$: C, 62.55, H, 8.90; S, 7.26. Found: C, 62.40; H, 9.03; S, 7.40.

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

Compound **9** (0.95 g, 2.3 x 10⁻³ mole) was dissolved in 10 ml of dry 1,2-dimethoxyethane and 0.57 g (1.4 x 10⁻³ mole) of Lawesson's Reagent was added. The mixture was stirred for 7 hours at room temperature and then an additional 0.57 g of Lawesson's Reagent was added to the reaction mixture. The mixture was refluxed gently for 28 hours. The reddish yellow solution was poured into 30 ml of water and extracted three times with 15 ml portions of dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was chromatographed on silica gel using ethanol/toluene (1:12) as eluant. The fractions including the objective compound were combined and evaporated to 20 ml and the precipitated brown solid was filtered. The filtrate was evaporated to give a yellow solid which was recrystallized from ethyl acetate and then methanol to give 0.12 g (12%) of **15** as yellow crystals, mp 145-148°; ir (potassium bromide): 3530, 3440, 3270, 1615, 755, 700 cm⁻¹; nmr (deuteriochloroform): δ 3.36-3.96 (m, 16H), 4.43 (s, 4H), 4.52-4.71 (m, 1H), 7.32 (s, 2H), 7.36 (s, 5H), 13.68 (broad, 1H, signal disappeared in dideuterium oxide).

Anal. Calcd. for $C_{21}H_{27}NO_5S \cdot H_2O$: C, 59.55; H, 6.90. Found: C, 59.71; H, 6.94.

Determination of the pK_a value for 13.

The proton ionization constant, pK_a, of **13** in water at 25° was determined to be 8.65 ±0.02 by potentiometric titration with tetramethylammonium hydroxide (an average of 3 determinations). The base was used as titrant and its concentration was determined to be 0.01026 M by titration against a standard solution of potassium hydrogen phthalate. Concentration of the crown solution was 0.0035 M. No spectator ions were added to adjust the ionic strength. The pH data were analyzed using a program (ACID) written for the IBM PC computer. The Debye Hückel limiting law was used to estimate activity coefficients.

X-Ray Determination.

A suitable single crystal of **13** was mounted on a Nicolet R3 automated diffractometer utilizing graphite monochromated Mo radiation (λ = 0.71073 Å). Lattice parameters and the orientation matrix were obtained using a least-squares procedure involving 21 centered reflections $4 < 2\theta < 21$. Crystal and structure solution data are listed in Table IV. Single crystal data were collected using a variable speed θ-2θ-scan technique. All data for which I < 1.5σ(I) were considered unobserved. A total of 1830 unique observed reflections were measured to a 2θ limit of 50° and were used in the structure solution process. The trial structure was

obtained using direct methods and was refined using a blocked cascading least-squares technique. All non-hydrogen atoms were refined anisotropically. Positions for hydrogen atoms bonded to carbon atoms were calculated based on stereochemical considerations and allowed to ride on the carbon atoms. Hydrogen atoms bonded to N1 and to the oxygen atoms of the two water molecules of solvation were located in difference map. It was not possible to locate one of the hydrogens bonded to OW2. These atoms were refined isotropically with the N-H bond fixed at 1.00 Å and the O-H bonds fixed at 0.98 Å. Weights were based on counting statistics. An empirical extinction correction was also applied to the data. Scattering factors were obtained from Volume IV of International

Tables for X-ray Crystallography [24]. All computer calculations were performed using the computer program package SHELXTL [25].

REFERENCES AND NOTES

[1] Permanent address for P. H.: Institute of Organic Chemistry, Technical University, Budapest, Hungary.

[2] Permanent address for H. K.: College of General Education, Kyushu University, Fukuoka, Japan.

[3] J. S. Bradshaw, D. A. Chamberlin, P. E. Harrison, B. E. Wilson, G. Arena, N. K. Dalley, J. D. Lamb, R. M. Izatt, F. G. Morin and D. M. Grant, *J. Org. Chem.*, **50**, 3065 (1985).

[4] J. S. Bradshaw, M. L. Colter, Y. Nakatsuji, N. D. Spencer, M. F. Brown, R. M. Izatt, G. Arena, P-K. Tse, B. E. Wilson, J. D. Lamb, N. K. Dalley, F. G. Morin and D. M. Grant, *J. Org. Chem.*, **50**, 4865 (1985).

[5] J. S. Bradshaw, Y. Nakatsuji, P. Huszthy, B. E. Wilson, N. K. Dalley and R. M. Izatt, *J. Heterocyclic Chem.*, **23**, 353 (1986).

[6] J. S. Bradshaw, R. B. Nielsen, P-K. Tse, G. Arena, B. E. Wilson, N. K. Dalley, J. D. Lamb, J. J. Christensen and R. M. Izatt, *J. Heterocyclic Chem.*, **23**, 361 (1986).

[7] J. F. Biernat, J. S. Bradshaw, B. E. Wilson, N. K. Dalley and R. M. Izatt, *J. Heterocyclic Chem.*, in press.

[8] J. S. Bradshaw, P. Huszthy and R. M. Izatt, *J. Heterocyclic Chem.*, in press.

[9] R. A. Bartsch, B. P. Czech, S. I. Kang, L. E. Stewart, W. Walkowiak, W. A. Charewicz, G. S. Heo and B. Son, *J. Am. Chem. Soc.*, **107**, 4997 (1985).

[10] R. C. Helgeson, J. M. Timko and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 3023 (1973).

[11] L. M. Dulyea, T. M. Fyles and D. M. Whitfield, *Can. J. Chem.*, **62**, 498 (1984).

[12] C. Thomas, C. Sauterey, M. Castaing, C. M. Gary-Bobo, J. M. Lehn and P. Plumere, *Biophys. Res. Commun.*, **116**, 981 (1983).

[13] C. M. Browne, G. Ferguson, M. A. McKervey, D. C. Mulholland, T. O'Connor and M. Parvez, *J. Am. Chem. Soc.*, **107**, 2703 (1985).

[14] S. R. Izatt, R. T. Hawkins, J. J. Christensen and R. M. Izatt, *J. Am. Chem. Soc.*, **107**, 63 (1985).

[15] R. M. Izatt, G. C. LindH, G. A. Clark, Y. Nakatsuji, J. S. Bradshaw, J. D. Lamb and J. J. Christensen, *J. Membrane Sci.*, in press.

[16] R. M. Izatt, G. C. LindH, G. A. Clark, J. S. Bradshaw, Y. Nakatsuji, J. D. Lamb and J. J. Christensen, *J. Chem. Soc., Chem. Commun.*, 1676 (1985).

[17] Y. Nakatsuji, J. S. Bradshaw, P-K. Tse, G. Arena, B. E. Wilson, N. K. Dalley and R. M. Izatt, *J. Chem. Soc., Chem. Commun.*, 749 (1985).

[18] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959).

[19] B. S. Pedersen, S. Scheibye, K. Clausen and S. -O. Lawesson, *Bull. Soc. Chim. Belg.*, **87**, 293 (1978).

[20] B. A. Jones, J. S. Bradshaw and R. M. Izatt, *J. Heterocyclic Chem.*, **19**, 551 (1982).

[21] J. D. Lamb, R. M. Izatt, D. G. Garrick, J. S. Bradshaw and J. J. Christensen, *J. Membr. Sci.*, **9**, 83 (1981).

[22] E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore and D. J. Cram, *J. Am. Chem. Sci.*, **99**, 2564 (1977).

[23] S. Mamedev, E. Sh. Mamedev, M. A. Avanesyan, A. A. Rzakulieva and R. Zeinalova, *Probl. Poluch. Poluprod. Prom. Org. Sin., Akad. Nauk SSSR, Otd. Obshch. Tekh. Khim., 90 (1967); Chem. Abstr.*, **68**, 29366 p (1968).

[24] International Tables for X-ray Crystallography, Vol. **4**, J. A. Ibers and W. C. Hamilton, eds, Kynoch Press, Birmingham, England, 1974, p 99.

[25] G. M. Sheldrick, "SHELXTL. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data", 4th revision, University of Göttingen, Federal Republic of Germany, 1983.