The structure was solved by direct methods using the NRC VAX crystal structure programs[26] and refined by full-matrix least-squares methods to final residuals of R_f and R_w of 0.052 and 0.032, respectively ($R_f = \Sigma(F_o - F_c)/\Sigma(F_o)$; $R_w = \Sigma(w(F_o - F_c)^2/\Sigma(wF_o)^2)$. The last least-squares cycle was calculated with 35 atoms, 237 parameters, and 1671 reflections. The final difference map showed no peaks greater than 0.250 e A^{-3}. Ten H atoms were found from difference maps, but the positions of the methyl hydrogens were calculated. The molecule shows no unusual features.

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Supplementary Material Available: Full final atomic positional parameters (Table I), complete bond lengths and bond angles for **6b** (Table II), thermal parameters (Table III), and an ORTEP-II plot of **6b** (4 pages). Ordering information is given on any current masthead page.

Proton-Ionizable Crown Compounds. 16. Synthesis, Structural Features, and Cation Transport Studies of Crown Ethers Containing the 4-Pyridone *N*-Hydroxide Subcyclic Group

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Pyridino-14-crown-4, two 4-(2-tetrahydropyranoxy)pyridino-14-crown-4 compounds, and the corresponding 4-(2-tetrahydropyranoxy)pyridino-15-crown-5 and -18-crown-6 compounds were oxidized to the *N*-oxide analogues by treatment with *m*-chloroperbenzoic acid. Upon hydrolysis, the tetrahydropyranoxy-substituted compounds became the *N*-hydroxy-4-pyridono-crown compounds in solution. A crystal structure determination of one of the new crowns showed that the 4-hydroxypyridine *N*-oxide was the stable form in the solid state. Of the alkali-metal cations, the *n*-octyl-substituted 1-hydroxy-4-pyridono-14-crown-4 compound transported lithium ions selectively in an aqueous metal hydroxide–methylene chloride–0.01 M aqueous hydrochloric acid bulk liquid membrane system.

We have reported a variety of proton-ionizable crown ligands. The majority of these compounds have the proton-ionizable group as part of the macroring. Examples shown in Figure 1 include crowns containing 4-pyridone (**1**),[1-3] triazolo (**2**),[4,5] and sulfonamido (**3**)[6-8] proton-ionizable units.

These new proton-ionizable crown compounds are effective transport agents for various cations in a water–methylene chloride–water bulk membrane system. Ligand **1** ($n = 1$) was found to be selective for potassium ions,[9] while **1** ($n = 0$) was found to be selective for lithium ions.[10] Ligand **2** proved to be selective for silver ions over all other metal ions tested.[11,12] Sulfonamido ligand **3** is an excellent carrier for all of the alkali metals.[8] In every case, transport of alkali-metal ions by these ligands occurred only when the source phase pH value was 13 or higher, indicating that ionization from the macrocycle was a necessary part of the transport process. Indeed, transport by ligand **3** occurred above pH values of 13.5, indicating that proton ionization of both N-H protons was necessary.[8] In general, the best metal ion transport results were observed where the receiving phase was acidic, showing that these transport systems were proton-driven.

Ligand **4**[3] was prepared with the hope that it would be even more selective for lithium ions than **1** ($n = 0$). The 14-crown-4 ligands have been shown to be selective complexing agents for lithium cations.[13] Compound **4**, how-

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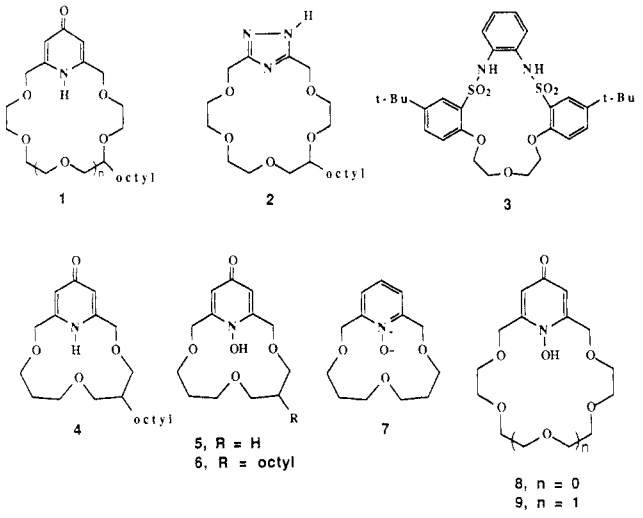

Figure 1. Structures of macrocyclic compounds.

ever, did not transport lithium ions, probably because complexation of lithium by **4** is so strong that the lithium ion is not released into the receiving phase. We decided to convert the 4-pyridono-14-crown-4 compounds into the 4-hydroxypyridine *N*-oxide (or 4-pyridone *N*-hydroxide) analogues for study as lithium transport agents. Compounds **5** and **6** were thus prepared along with *N*-oxide **7** for comparison purposes. Compounds **8** and **9** were prepared to compare their properties to those of the smaller macroring *N*-oxide compounds.

Pyridino-crown *N*-oxides have been reported by Vögtle and his coworkers.[14-17] Macrocyclic ligands containing the 4-hydroxypyridine *N*-oxide group have not been reported. Shaw first prepared 4-hydroxypyridine *N*-oxide in 1949.[18] He decided that it had the 4-pyridone *N*-hydroxide form by analogy to the 2-hydroxypyridine *N*-oxide, which was shown to be in the 2-pyridone form.[18] Others have shown that in aqueous solutions, the 4-hydroxypyridine *N*-oxide was a mixture of the hydroxy *N*-oxide and oxo *N*-hydroxide forms.[19,20]

The present paper reports the synthesis and structure of compounds **5–9** and transport properties of **6**. In solution, the new crowns, **5**, **6**, **8**, and **9** have the oxo *N*-hydroxide structures shown in Figure 1. A crystal structure determination of **5** showed that it possesses the 4-hydroxypyridine *N*-oxide structure in the solid state.

Experimental Section

Infrared (IR) spectra were obtained on a Beckman Acculab 2 spectrophotometer or a Matson FTIR instrument. The nuclear magnetic resonance (NMR) spectra were obtained on a JEOL FX90Q or a Varian Gemini 200-MHz spectrometer in deuteriochloroform. Crystal structure determinations were done on a Nicolet R3 autodiffractometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected.

3,7,11-Trioxa-17-azabicyclo[11.3.1]heptadeca-13,16-dien-15(17*H*)-one 17-Hydroxide (5). 3,7,11-Trioxa-17-azabicyclo-[11.3.1]heptadeca-15-(2-tetrahydropyranoxy)-13,15,1(17)-triene (3.0 g, 9.9 mmol) (prepared as reported[3] except the crude product was not treated with *p*-toluenesulfonic acid but was purified by basic alumina chromatography), 3.3 g (10.7 mmol) of *m*-chloroperbenzoic acid, and 40 mL of methylene chloride were allowed to stand at room temperature for 1 h. The solvent was removed under vacuum, and the crude product was passed through a short silica gel column, using 10:1 hexane–ethanol as eluant. The product was recrystallized (ethyl acetate and ethanol) to give fine white crystals: 0.25 g (10%); mp 205–206 °C (dec); IR (KBr) 3250, 1625 cm^{-1}; NMR δ 1.80 (q, 4 H), 3.46 (m, 8 H), 4–5 (broad, 4 H), 5.6 (broad, 1 H, disappeared in D_2O), 6.36 (s, 2 H). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11. Found: C, 57.75; H, 7.26.

5-Octyl-3,7,11-trioxa-17-azabicyclo[11.3.1]heptadeca-13,16-dien-15(17*H*)-one 17-Hydroxide (6). 5-Octyl-3,7,11-trioxa-17-azabicyclo[11.3.1]heptadeca-15-(2-tetrahydropyranoxy)-13,15,1(17)-triene (2.34 g, 5.2 mmol) (prepared as reported[3] except the crude product was not treated with *p*-toluenesulfonic acid but was purified by basic alumina chromatography), 1.8 g (5.3 mmol) of *m*-chloroperbenzoic acid, and 35 mL of methylene chloride were reacted as above for **5** to give 0.29 g (15%) of fine white crystals: mp 147–148.5 °C; IR (KBr) 3225, 1625 cm^{-1}; NMR δ 0.88 (t, 3 H), 1.24 (s, 14 H), 1.84 (m, 3 H), 3.50 (m, 8 H), 4.48 (s, 2 H), 4.0–5.0 (broad, 3 H, peak decreases in size in D_2O), 6.18 (s, 1 H), 6.36 (s, 1 H). Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25. Found: C, 66.36; H, 9.37.

3,7,11-Trioxa-17-azabicyclo[11.3.1]heptadeca-13,15,1(17)-triene 17-Oxide (7). 3,7,11-Trioxa-17-azabicyclo[11.3.1.]heptadeca-13,15,1(17)-triene[3] (0.75 g, 3.2 mmol), 1.1 g (6.3 mmol) of *m*-chloroperbenzoic acid, and 15 mL of methylene chloride were reacted as above for **5** to give 0.49 g (61%) of white prisms (recrystallized from ethyl acetate): mp 113–114.5 °C; NMR δ 1.68 (m, 4. H), 3.42 (m, 8 H), 4.0–5.5 (broad, 4 H), 7.48 (complex m, 3 H). Anal. Calcd for $C_{13}H_{19}NO_4 \cdot H_2O$: C, 57.55; H, 7.80; mol wt 271.31. Found: C, 57.58; H, 7.55; mol wt 273.4.

3,6,9,12-Tetraoxa-18-azabicyclo[12.3.1]octadeca-14,17-dien-16(18*H*)-one 18-Hydroxide (8). 3,6,9,12-Tetraoxa-18-azabicyclo[12.3.1]octadeca-16-(2-tetrahydropyranoxy)-14,16,1-(18)-triene (0.9 g, 2.5 mmol) (prepared as reported[1] except the crude product was not treated with *p*-toluenesulfonic acid but was purified by basic aluminum oxide chromatography (50:1 toluene–ethanol)) and 0.86 g (5 mmol) of *m*-chloroperbenzoic acid were reacted as above for **5**. The product was passed through a silica gel column (methanol) to give 0.03 g (4%) of **10**: mp 135 °C; IR (KBr) 3320, 1625 cm^{-1}; NMR δ 3.60 (s, 8 H), 3.80 (m, 4 H), 4.55 (s, 4 H), 6.40 (s, 2 H), (the peak for the OH group was not observed); MS *m/z* 286. Anal. Calcd for $C_{13}H_{19}NO_6 \cdot H_2O$: C, 51.48; H, 6.98. Found: C, 51.68; H, 6.64.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-17,20-dien-19(21*H*)-one 21-Hydroxide (9). 3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-19-(2-tetrahydropyranoxy)-17,19,1-(21)-triene (1 g, 2.5 mmol) (prepared as reported[1] except the crude product was not treated with *p*-toluenesulfonic acid but was purifed by basic alumina chromatography (50:1 toluene–ethanol)) and 0.86 g (5 mmol) of *m*-chloroperbenzoic acid were reacted as above for **5**. The product was passed through a silica gel column (methanol) to give 0.04 g (5%) of **9**: mp 166 °C; IR (KBr) 3325, 1625 cm^{-1}; NMR δ 3.32 and 3.38 (two s, 16 H), 4.22 (s, 4 H), 6.28 (s, 2 H) (the peak for the OH group was not observed); MS *m/z* 330. Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04. Found: C, 54.54; H, 6.98.

Temperature-Dependent NMR Studies. The NMR spectra at room temperature for compounds **5**, **6**, and **7** exhibited a broad peak between δ 4.0 and δ 5.5. The NMR probe temperature was lowered until two sets of peaks of equal intensity were observed. The peaks appeared at δ 4.16 and 5.09 at −30 °C for **5**, δ 4.12 and 5.21 at −30 °C for **6**, δ 4.26 and 5.46 at −30 °C for **7**, and δ 4.0 and 5.02 at −65 °C for **8** and **9**. The aromatic peak at δ 6.40 for **8** also separated to give peaks at δ 6.38 and 7.08 at −65 °C. The probe temperature was allowed to rise, and successive spectra were run until the approximate peak coalescence temperature was achieved. The approximate coalescence temperatures were 19 °C for **5**, 23 °C for **6**, 23 °C for **7**, and −30 °C for **8** and **9**. The free energy of activation ($\Delta G^{\ddagger}$) values were calculated[21,22] and are shown in Table I.

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Table I. Coalescence Temperatures and Free Energies of Activation for the Conformational Transformations of 5–9[a]

compd	T_c, °C	$\Delta G^{\ddagger}$, kcal/mol
5	19	15.5
6	23	15.9
7	23	15.9
8	−30	12.8
9	−30	12.9

[a] Both JEOL FX-90Q and Varian Gemini 200-MHz NMR spectrometers were used to record spectra in CD_2Cl_2 or $CDCl_3$. The uncertainties of the $\Delta G^{\ddagger}$ values are ±0.3.

Table II. Crystal and Experimental Data for 5 and 7

	5	7
formula	$C_{13}H_{19}NO_5 \cdot H_2O$	$C_{13}H_{19}NO_4 \cdot H_2O$
fw	287.31	271.31
$F(000)$	616	584
crystal size, mm	0.1 × 0.2 × 0.4	0.3 × 0.3 × 0.2
space group	$P2_1/n$	$P2_1/n$
a, Å	8.189 (6)	7.826 (4)
b, Å	14.625 (10)	14.586 (5)
c, Å	12.070 (8)	12.282 (8)
β, deg	102.16 (5)	101.68 (5)
V, Å^3	1412 (1)	1373 (1)
Z	4	4
ρ_x, g cm^{-3}	1.35	1.31
μ, cm^{-1}	1.00	0.90
$(\sin\theta)/\lambda$	0.59	0.54
total data	2910	2128
obsd unique data	1419	1272
unobsd data ($F < 3\sigma(F)$)	1082	528
R_m	0.02 (7)	0.02 (4)
R	0.077	0.050
R_w	0.040	0.043
GOF	1.71	1.38
G in weights	$<10^{-5}$	2.2×10^{-4}
largest peaks in Δ map	0.34, −0.36	0.19, −0.24

X-ray Structural Determinations. Crystal and intensity data for both **5** and **7** were obtained with a Nicolet R3 automated diffractometer using Mo Kα (λ = 0.71073 Å) radiation. Suitable crystals were chosen for each study and used without drying. The lattice parameters and orientation matrix for each crystal were obtained by using a least-squares procedure, with each determination using 20 carefully centered reflections. The crystal and experimental data are summarized in Table II. Intensity data for the compounds were collected by using a variable speed θ–2θ scan procedure. The structures were solved by direct methods. Difference maps revealed that each crystal contained a water of hydration. All non-hydrogen atoms were refined anisotropically. Positions for hydrogen atoms bonded to carbon atoms were calculated based on stereochemical considerations with the isotropic thermal parameters of these atoms set at 1.2 times the initial equivalent isotropic thermal parameter of the carbon atom to which it is bonded. The parameters of these hydrogen atoms were not refined. The hydrogen atoms of the water of hydration of each compound as well as HO16 of **5** were located in difference maps. The positional and isotropic parameters of these hydrogens in **7** were refined but only the isotropic thermal parameter of water hydrogens and HO16 of **5** were refined. Weights based on counting statistics were applied to both compounds during the refinement process and in addition an empirical extinction parameter was applied to the data of **5**. The resulting R values were R = 0.050 and R_w = 0.043 for **7** and R = 0.077 and R_w = 0.040 for **5**. All computer programs used in the solution and display of the structures are contained in the SHELXTL[23] program package supplied with the Nicolet instrument. Scattering factors were obtained from the literature.[24]

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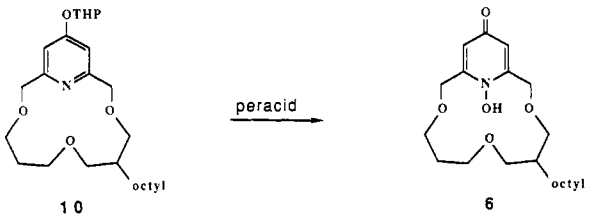
Table III. Li^+ Fluxes[a] in a Bulk Water–Methylene Chloride–Water Liquid Membrane[b] System Using 1[c] (n = 0) and 6 as Carriers

carrier	receiving phase pH	source phase pH 11	12	13	13.5	14
1 (n = 0)	7	2	4	50	2313	4254
	1.5	0	0	32	785	929
6	7	1	0	32	44	48
	1.5	0	0	95	642[d]	422

[a] J_m = mol·10^{-8}·s^{-1}·m^{-2}; standard deviations are ±15% except as noted. [b] Phase compositions: source, 1.0 M in Li^+ using appropriate amounts of $LiNO_3$ and LiOH to achieve the initial source phase pH; membrane, 0.001 M in **1** (n = 0) or **6** in methylene chloride; receiving, initial pH of 7 (H_2O) or 1.5 (HNO_3), as indicated. [c] Data for **1** (n = 0) were reported in ref 10. [d] Standard deviation was ±50%.

Scheme I. Preparation of *N*-Hydroxypyridono-crowns



Cation Transport Studies of 6. Membrane transport experiments were carried out with the H_2O–CH_2Cl_2–H_2O bulk liquid membrane system described previously.[9,10,25] The metal nitrates and hydroxides were obtained from commercial sources in the highest grade available and were used without further purification. The metal solutions were prepared with distilled deionized water.

Source phases of different pH were prepared from appropriate amounts of MNO_3 and MOH. After 24 h, the receiving phase was sampled and analyzed for cation concentration using a Perkin-Elmer 603 atomic absorption spectrometer. Each experiment was repeated at least three times, and the results reported in Table III are the average of the three determinations. The standard deviation from the mean among the values in each experiment is <15%.

Results and Discussion

The macrocyclic compounds containing the 4-pyridone *N*-hydroxide subcyclic unit were prepared by oxidizing the corresponding 4-(tetrahydropyranoxy)pyridino-crowns as shown in Scheme I. Compound **7**, which has no oxygen substituent on the pyridine ring, was prepared in a reasonably good yield (61%). Oxidation of the acid-labile THP-containing compounds gave significantly lower yields, particularly in the case of the larger ring compounds (**8** and **9**). It is instructive to note that 4-pyridone compounds do not oxidize to the *N*-oxide product under the conditions of our oxidation reaction. Starting THP-blocked crowns (**10** for example) were prepared as reported[1,3] except that the crude product mixture was neutralized and passed through basic alumina.

The proposed structural formulas of the new compounds (**5–9**), as shown in Figure 1, are consistent with data obtained from NMR and IR spectra and combustion analyses. A solid crystal of **5** showed a different structure as will be discussed below. The NMR spectra in $CDCl_3$ clearly show the 4-pyridone *N*-hydroxide subcyclic group in **5**, **6**, **8**, and **9**. The signals in the NMR spectrum for *N*-oxide compound **7** attributable to the aromatic hydrogen atoms appear at δ 7.48. The pyridone hydrogens for com-

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Table IV. Positional Parameters (×10⁴) and Thermal Parameters (Å² × 10³) for the Atoms of 5 with Esd Values in Parentheses

atom	x	y	z	U
N1	3407 (4)	2848 (3)	-24 (3)	30 (1)[a]
O1	4605 (3)	2536 (2)	830 (2)	39 (1)[a]
C2	3135 (5)	3759 (3)	-129 (3)	26 (2)[a]
C3	3940 (5)	4370 (3)	840 (3)	34 (2)[a]
O4	3403 (4)	4165 (2)	1848 (3)	34 (1)[a]
C5	1682 (5)	4353 (3)	1782 (3)	39 (2)[a]
C6	1197 (5)	4069 (3)	2866 (4)	39 (2)[a]
C7	1502 (6)	3067 (3)	3131 (4)	43 (2)[a]
O8	495 (4)	2531 (2)	2272 (3)	40 (1)[a]
C9	779 (6)	1582 (3)	2454 (4)	43 (2)[a]
C10	-198 (6)	1051 (3)	1465 (4)	45 (2)[a]
C11	327 (5)	1266 (3)	364 (4)	46 (2)[a]
O12	2041 (3)	1026 (2)	463 (2)	37 (1)[a]
C13	2698 (5)	1240 (3)	-504 (3)	33 (2)[a]
C14	2539 (5)	2233 (3)	-777 (4)	28 (2)[a]
C15	1478 (5)	2566 (3)	-1728 (3)	32 (2)[a]
C16	1262 (5)	3494 (3)	-1909 (4)	30 (2)[a]
O16	268 (4)	3860 (2)	-2835 (2)	45 (1)[a]
HO16	98	3418	-3453	174 (25)
C17	2072 (5)	4096 (3)	-1074 (3)	29 (2)[a]
OW	7714 (4)	3422 (2)	765 (3)	66 (2)[a]
HOW1	8477	3107	1352	149 (22)
HOW2	6796	2898	639	144 (21)
H3A	3659	4994	636	36
H3B	5130	4294	973	36
H5A	1484	4997	1665	44
H5B	1023	4020	1160	44
H6A	1838	4421	3477	45
H6B	30	4193	2803	45
H7A	1224	2931	3847	48
H7B	2658	2928	3167	48
H9A	1948	1455	2533	50
H9B	430	1402	3133	50
H10A	-32	410	1620	56
H10B	-1361	1196	1381	56
H11A	184	1907	205	48
H11B	-348	922	-240	48
H13A	3857	1073	-359	43
H13B	2098	898	-1140	43
H15	876	2146	-2276	36
H17	1885	4743	-1160	37

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

pounds **5**, **8**, and **9** cause NMR signals at δ 6.35 ± 0.07, and nonsymmetrical **6** causes NMR signals for two pyridone ring hydrogen atoms, one at δ 6.18 and the other at δ 6.36. The NMR signal at δ 6.35 was also observed in the NMR spectrum of **5** taken in CD_3OD. The NMR signals at δ 6.35 are indicative of the 4-pyridone structural feature, in contrast to the usual pyridine structure, where the signals are shifted downfield. 2,6-Dimethylpyridine, for example, has NMR signals for the aromatic hydrogens at δ 6.97 and 7.45. The non-*N*-oxide pyridino- and pyridono-crown compounds also gave these same relative chemical shift values in the NMR spectra. Thus, the NMR signals for the aromatic hydrogens of 4-hydroxypyridino and 4-(benzyloxy)pyridino diester crowns were observed at δ 7.46 and 7.92, respectively,[26] while the aromatic signals for **1** (n = 1), a pyridono-crown, were observed at δ 6.20.[1]

The crystal structure of **5** and **7** are shown in Figures 2 and 3, respectively. The atomic parameters for **5** and **7** are listed in Tables IV and V, respectively, while the bond lengths and angles of the two compounds are compared in Table VI. The structure of **7** (Figure 3) is the

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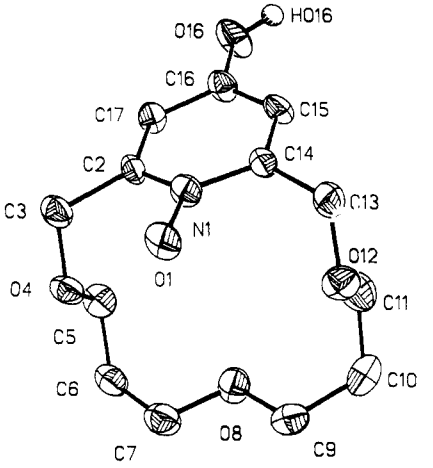

Figure 2. Computer drawing of **5** with the water of hydration and all hydrogen atoms except HO16 omitted for clarity.

Table V. Positional Parameters (×10⁴) and Thermal Parameters (Å² × 10³) for the Atoms of 7 with Esd Values in Parentheses

atom	x	y	z	U
N1	3211 (3)	7201 (2)	1633 (2)	40 (1)[a]
O1	3911 (3)	7532 (2)	2607 (2)	57 (1)[a]
C2	3079 (4)	6278 (2)	1487 (2)	37 (1)[a]
C3	3961 (4)	5684 (2)	2427 (3)	50 (1)[a]
O4	5799 (3)	5774 (1)	2641 (2)	47 (1)[a]
C5	6538 (4)	5525 (2)	1716 (3)	49 (1)[a]
C6	8466 (4)	5730 (2)	1993 (3)	51 (1)[a]
C7	8857 (4)	6718 (2)	2286 (3)	50 (1)[a]
O8	8216 (3)	7280 (1)	1346 (2)	49 (1)[a]
C9	8379 (4)	8223 (2)	1639 (3)	55 (1)[a]
C10	7623 (4)	8804 (2)	643 (3)	58 (1)[a]
C11	5688 (4)	8698 (2)	260 (3)	55 (1)[a]
O12	4865 (3)	8963 (1)	1140 (2)	57 (1)[a]
C13	3053 (4)	8780 (2)	953 (3)	60 (1)[a]
C14	2636 (4)	7787 (2)	767 (3)	42 (1)[a]
C15	1769 (4)	7436 (2)	-236 (2)	45 (1)[a]
C16	1528 (4)	6507 (2)	-383 (3)	45 (1)[a]
C17	2224 (4)	5930 (2)	478 (2)	45 (1)[a]
OW	2121 (4)	8504 (2)	4070 (3)	76 (1)[a]
HOW1	2608 (53)	8250 (29)	3633 (32)	94 (17)
HOW2	2473 (59)	8276 (33)	4693 (37)	126 (21)
H3A	3664	5056	2245	62
H3B	3550	5852	3085	62
H5A	6361	4883	1566	60
H5B	5995	5872	1075	60
H6A	8957	5579	1360	65
H6B	8996	5358	2614	65
H7A	10095	6799	2510	59
H7B	8303	6889	2885	59
H9A	7761	8343	2225	67
H9B	9590	8372	1889	67
H10A	8176	8635	42	70
H10B	7870	9436	833	70
H11A	5414	8070	64	65
H11B	5288	9082	-375	65
H13A	2618	8982	1589	71
H13B	2485	9116	308	71
H15	1328	7845	-840	54
H16	887	6265	-1073	56
H17	2115	5279	377	54

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

pyridine *N*-oxide as expected. However, compound **5**, which contains a pyridone unit in solution as indicated by the NMR spectral results mentioned above, has a 4-hydroxypyridine *N*-oxide unit in the solid state. This is apparent from examination of the bond lengths in Table VI. Specifically, the bond lengths C14–C15, C15–C16, C16–C17, and C17–C2 are essentially the same in the two

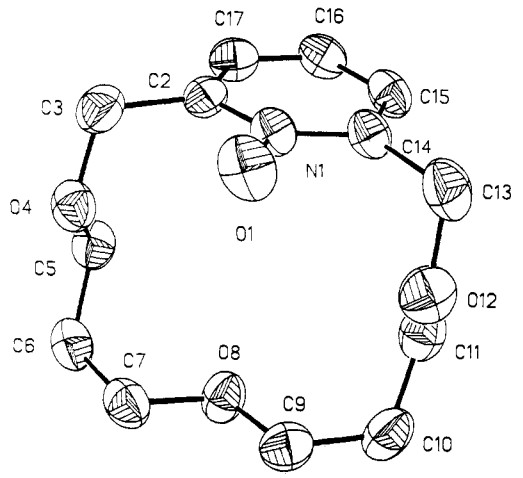

Figure 3. Computer drawing of **7** with the water of hydration and all hydrogen atoms omitted for clarity.

Table VI. Bond Lengths (Å) and Angles (Deg) of 5 (Figure 2) and 7 (Figure 3) with Esd Values in Parentheses

	5		7	
1 2 3	1–2 bond length, Å	1–2–3 angle, deg	1–2 bond length, Å	1–2–3 angle, deg
O1 N1 C2	1.344 (4)	119.0 (3)	1.304 (3)	119.6 (2)
C14 N1 O1	1.367 (5)	118.7 (3)	1.368 (4)	119.6 (2)
N1 C2 C3	1.352 (6)	118.3 (3)	1.359 (4)	117.5 (2)
C2 C3 O4	1.509 (6)	112.2 (4)	1.496 (4)	112.5 (3)
C3 O4 C5	1.410 (5)	113.4 (3)	1.415 (4)	113.0 (2)
O4 C5 C6	1.421 (5)	109.8 (3)	1.423 (4)	108.6 (2)
C5 C6 C7	1.504 (6)	113.0 (4)	1.507 (5)	113.0 (3)
C6 C7 O8	1.509 (7)	109.7 (3)	1.501 (5)	109.8 (2)
C7 O8 C9	1.418 (5)	112.2 (3)	1.422 (4)	110.7 (2)
O8 C9 C10	1.417 (6)	109.9 (3)	1.421 (4)	109.8 (2)
C9 C10 C11	1.505 (6)	112.8 (4)	1.507 (4)	113.7 (3)
C10 C11 O12	1.513 (7)	109.4 (3)	1.500 (5)	108.6 (2)
C11 O12 C13	1.427 (5)	114.4 (3)	1.419 (4)	114.8 (2)
O12 C13 C14	1.419 (5)	111.5 (4)	1.415 (4)	112.9 (3)
C13 C14 N1	1.490 (6)	119.1 (3)	1.492 (4)	117.4 (2)
C13 C14 C15	*a*	122.7 (4)	*a*	123.4 (3)
N1 C14 C15	*a*	118.1 (4)	*a*	119.2 (3)
C14 C15 C16	1.374 (5)	121.2 (4)	1.379 (4)	120.9 (3)
C15 C16 C17	1.380 (6)	118.7 (4)	1.375 (5)	118.6 (3)
C16 C17 C2	1.396 (6)	119.7 (4)	1.375 (4)	120.7 (3)
C17 C2 C3	1.372 (5)	121.9 (4)	1.380 (4)	122.9 (3)
C17 C2 N1	*a*	119.7 (4)	*a*	119.5 (2)
C2 N1 C14	*a*	122.2 (3)	*a*	120.8 (2)
O16 C16 C15	1.347 (5)	123.8 (4)		
O16 C16 C17	*a*	117.4 (4)		

[a] Value listed earlier in table.

compounds (Table VI). In neither case is there evidence of carbon–carbon double bonds in the pyridine ring. Also the O16–C16 bond of **5** [1.347 (5) Å] is clearly a single bond, which eliminates the possibility of a pyridone unit. Thus, the 4-hydroxypyridine *N*-oxide of the crystal of **5** rearranges to the 4-pyridone *N*-hydroxide form in solution.

The structures of **5** and **7** are similar, the major difference being the replacement of the O–H group in **5** (Figure 2) with a hydrogen in **7** (Figure 3). The lattice parameters of the two crystals are also similar but the compounds are not isostructural. The major difference in the two crystal structures is in the hydrogen-bonding arrangement. The hydrogen-bonding data are listed in Table VII. In both **5** and **7**, molecules are linked by hydrogen bonds involving the water molecule from O1 of one molecule to O8 of a symmetry-related molecule. In **5**, there is an additional hydrogen bond linking O16 and O1 of another molecule.

Because of the unexpected tautomerization of **5** from the 4-pyridone *N*-hydroxide form in solution to the 4-hydroxypyridine *N*-oxide form in the solid state, the difference map in the regions of O1 and O16 were examined. As indicated in Table VII the interatomic distance between O1 and O16 of a symmetry-related molecule is short [2.588 (6) Å]. There are small peaks in the difference map near both oxygen atoms which could correspond to hydrogen positions. However, the peak near O16 is larger than the one near O1 (0.44 e Å^{-3} compared to 0.35 e Å^{-3}); thus the peak near O16 was chosen as the proper hydrogen position. This choice, which would require the six-member ring to be a 4-hydroxypyridine, is in agreement with the choice based on the geometry of the ring.

Table VII. Hydrogen Bond Data

D H A	D–H, Å	H···A, Å	D–H···A, deg	symmetry translation
		Compound **7**		
OW HOW1 O1	2.06 (4)	2.867 (5)	176 (3)	*x*, *y*, *z*
OW HOW2 O8	2.15 (4)	2.981 (4)	176 (4)	$-0.5x$, $1.5 - y$, $0.5 + z$
		Compound **5**		
OW HOW2 O1	1.93 (5)[a]	2.872 (5)	146 (5)[a]	*x*, *y*, *z*
OW HOW1 O8	1.98 (5)[a]	2.907 (5)	163 (5)[a]	$1 + x$, *y*, *z*
O16 HO16 O1	1.65 (5)[a]	2.588 (5)	161 (5)[a]	$-0.5 + x$, $0.5 - y$, $-0.5 + z$

[a] Uncertainties estimated because the positional parameters of the hydrogen atoms were not refined.

The rearrangement of macrocycle **5** from the 4-pyridone *N*-hydroxide form in solution to the 4-hydroxypyridine *N*-oxide form in the solid state is interesting. The fact that the 4-pyridone *N*-oxide form is the stable one in solution indicates that the 4-hydroxypyridine form is a stronger acid than the *N*-hydroxide form. In the solid state, the oxyen atom in the 4-position of one symmetry-related molecule is very close to the pyridine *N*-oxide oxygen atom of the other molecule. Thus, it would be easy for the hydrogen on the *N*-hydroxide of one molecule in solution to transfer to the pyridone oxygen of the other molecule as crystallization takes place. This would cause the pyridone *N*-hydroxide form to change to the hydroxypyridine *N*-oxide form. A driving force for this reaction could be the added stability of an aromatic system over the corresponding diene system.

Compounds **5–7** are conformationally labile in solution at room temperature. For **5–7**, the NMR peak at δ 4.52 attributable to the hydrogens on the carbons next to the pyridone ring is fairly sharp at 40 °C. The peak became flat at about 19 °C (coalescence temperature, T_c) and separated into two sets of doublets at 0 °C and below. Compounds **8** and **9** gave a more complex set of peaks at low temperatures, but a coalescence of peaks was observed at about −30 °C. Table I lists the coalescence temperatures and calculated free energies of activation ($\Delta G^{\ddagger}$)[21,22] for the conformational transformations.

The $\Delta G^{\ddagger}$ values shown in Table I are similar to those found for conformational inversions in the calixarene compounds.[27] The calix[4]arene, with an inside macroring cavity of 16 atoms, had a $\Delta G^{\ddagger}$ value of 15.7 kcal·mol^{-1} while the larger calix[5]arene and calix[6]arene, with cavities of 20 and 24 atoms, respectively, had $\Delta G^{\ddagger}$ values of 13.2 and 13.3 kcal·mol^{-1}, respectively. With the calixarenes, the free energy barrier was determined to be rotation of one of the aryl rings in a direction that brings the hydroxyl group through the macroring cavity.[27] The free energy barrier in compounds **5–7** is on the same order as that of the

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smallest calixarene. Here, there would be a barrier to the free rotation of the pyridine ring in the direction that takes the *N*-oxide (**7**) or *N*-hydroxide (**5**, **6**) through the cavity. Compounds **8** and **9** have larger cavities, resulting in lower barrier energies. Compounds **5**, **6**, **8**, and **9** are known to be in the *N*-hydroxide form in solution (see NMR discussion above) while **7** is an *N*-oxide. It is not understood why the conformational barriers for the *N*-hydroxides and *N*-oxide compounds are the same. The tetra-*O*-methyl calix[4]arene, where all the phenolic OH groups were methylated, had about the same barrier to rotation as did the parent calix[4]arene.[27] Likewise in our case, the addition of a hydrogen to the *N*-oxide oxygen for **7** to have **5** or **6** evidently does not cause more steric hindrance for the rotational process.

Compound **6** was found to be an effective transport agent for lithium ions in a water–methylene chloride–water bulk liquid membrane system.[9,10] We have reported that **1** ($n = 0$) is an excellent transporting agent for lithium ions. A comparison of flux values for the transport of lithium ions by **1** ($n = 0$) and **6** is given in Table III. It is apparent that different mechanisms are operative for the transport of lithium ions by **1** ($n = 0$) and **6**. Both crowns exhibited the best transport at high source phase pH values since they need to be ionized before complexation can occur. However, **1** ($n = 0$) gave the best transport into a receiving phase that was neutral, while **6** transported best into an acidic receiving phase. The transport rate for **6** was much lower than that for **1** ($n = 0$). In single-cation systems, crown **6** did not transport to any significanct degree any other cation studied except lithium as mentioned above and silver, which was transported at a flux <1 mol·10^{-6} $s^{-1}\cdot m^{-2}$. Crown **1** ($n = 0$) was selective for lithium ions over all other alkali-metal cations in competitive transport in the bulk liquid membrane system.[10] Compound **6** was likewise a selective transporter of lithium over other alkali-metal cations in competitive cation experiments into a water receiving phase with selectivities of $Li^+/Na^+ = 22$, $Li^+/Rb^+ = 54$, and $Li^+/Cs^+ = 10$. Competitive transport into an acid receiving phase also showed Li^+ selectivity but the deviations were too large to quantify the results.

When crown **1** ($n = 0$) is ionized, the resulting cavity is open and the pyridone ring contains a negative charge. The resulting macroring is able to accommodate a lithium ion in the cavity. Crown **6** would ionize to give a cavity with an *N*-oxide in close proximity which would interfere with an incoming cation so that complexation probably takes place above the ring cavity. A similar complexing mode was observed by Browne and co-workers for an 18-crown-6 containing an intraannular phenolic group.[28] They observed that their carrier transported all the alkali-metal ions in single-cation experiments, possibly because an 18-membered macroring was used. The smaller ring cavity in the case of **6** would be the best size for the lithium ion.

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Electrochemical Oxidation of 5-Hydroxytryptamine in Acidic Acetonitrile

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The electrochemical oxidation of 5-hydroxytryptamine (AH) in acidic acetonitrile yields predominantly (80%) a 3,4′ dimer (indoleninium, indole) whose structure has been established by means of ^1H and ^{13}C NMR and other analytical techniques. On the basis of cyclic voltammetry a mechanism is proposed. The initial heterogeneous one-electron abstraction (standard redox potential $E°$) produces a C(3)• radical cation $AH^{•+}$ and is followed by a 3,4′ radical–substrate coupling yielding a dimer radical cation $DH^{•+}$. A disproportionation-like second-electron transfer occurring in solution between $AH^{•+}$ and $DH^{•+}$ gives AH (half-regeneration) and DH_2^{2+}, which deprotonates at position 4′, that deprotonation being the rate-determining step of the whole process. An estimation of $E°$ is possible: $+925 < E° < +950$ mV vs SCE.

The biological interest of studying the oxidation of 5-hydroxytryptamine (5HT) has been summarized in a recent paper.[2] The authors described the products formed at micromolar concentrations through electrochemical oxidation controlled to a significant extent by the adsorption of reactant and product(s), and they also proposed a mechanism for the electrochemical process. Their experiments were carried out in acidic (pH ~2) aqueous media using pyrolytic graphite electrodes.

The present paper deals with the electrochemical oxidation of 5HT under conditions that permit the obtention of signals free of adsorption interference and allow mechanistic deductions through careful cyclic voltammetric analysis. The results we report show that use of a nonaqueous solvent such as acetonitrile (ACN) and platinum electrodes prevents the occurrences of appreciable adsorption and electrode fouling, even when the 5HT concentration lies in the millimolar range. Addition of 1 M $HClO_4$ is motivated by two reasons: The final products are probably less prone to spontaneous oxidation in such

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