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New Proton-ionizable Macrocyclic Ligands. Synthesis, Basicity, Reactions, and Structures of Two Aza Crown Ethers containing the 4-Hydroxypyridine Unit

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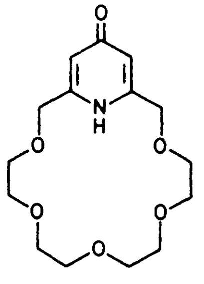
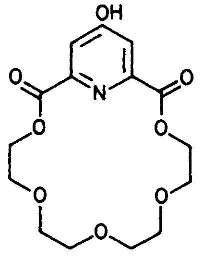
Two new reactive aza crown ethers, (**1**) and (**2**), containing the 4-hydroxypyridine unit have been prepared and found to be different with respect to pK(H_2O) values for H_2L^+, structures of the hydrates of HL, and complex formation with benzylamine and the benzylammonium ion.

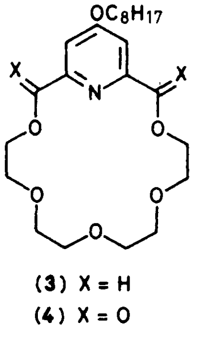
Crown ethers containing reactive groups are important as intermediates for the preparation of functionalized crown derivatives such as lariat ethers, bis(crown ethers), synthetic ionophores, immobilized crown ethers, and crown polymers.[1] Interest in these applications has resulted in the development of a variety of synthetic procedures for the preparation of hydroxymethyl crown ethers, which are representative of such compounds.[2] We report here the synthesis of two new macrocycles (**1**) and (**2**). Each of these compounds contains the 4-hydroxypyridine unit, but their reactions, basicity, and structures are distinctly different.



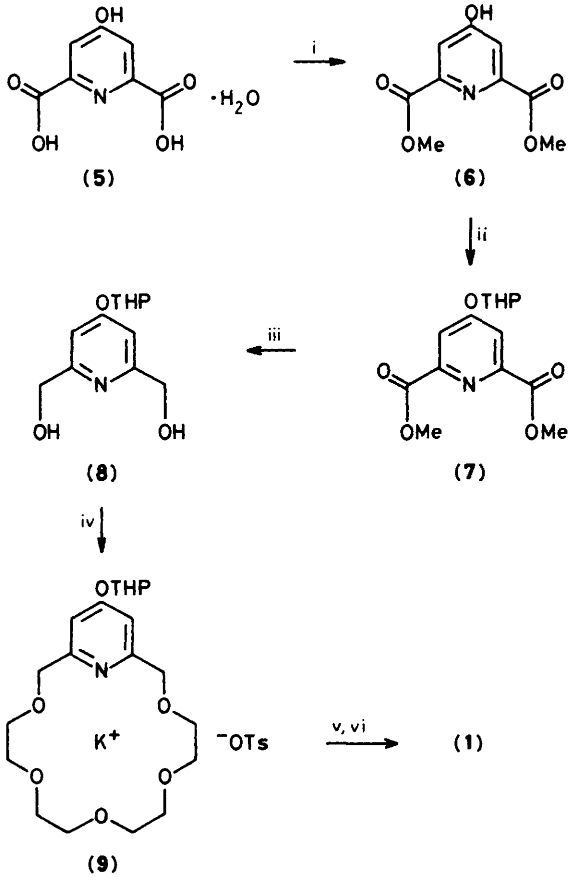
(**1**)



(**2**)



(**3**) X = H
(**4**) X = O

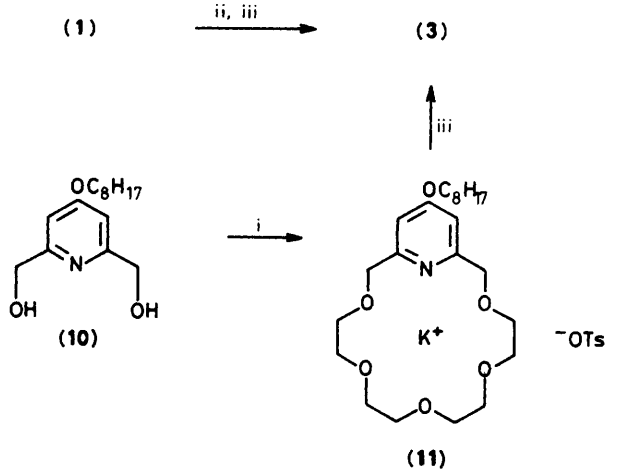


Scheme 1. *Reagents and conditions:* i, MeOH/H_2SO_4, reflux; ii, 2,3-dihydropyran, pyridinium toluene-*p*-sulphonate, CH_2Cl_2, room temp.; iii, $NaBH_4$, ethanol, reflux; iv, tetraethylene glycol bis(toluene-*p*-sulphonate), Bu^{t}OK, Bu^{t}OH, dioxane, reflux, 24 h; v, MeOH, toluene-*p*-sulphonic acid, reflux; vi, alumina column chromatography, CH_2Cl_2–$CHCl_3$ = 1 : 1.

Table 1. pK_n, ΔH_n, and $T\Delta S_n$ Values[a] valid in H_2O at 25 °C for proton ionization from the protonated forms of (**1**) and (**2**), H_2L^+.

Compound	Reaction	n	pK_n	ΔH_n/kcal mol^{-1}	$T\Delta S_n$/kcal mol^{-1}
(**1**)	$H_2L^+ = HL + H^+$	1	3.10±0.03	0.99±0.02	−3.24
(**1**)	$HL = L^- + H^+$	2	10.98±0.02	9.25±0.05	−5.72
(**2**)	$H_2L^+ = HL + H^+$	1	1.70[b]	−0.35	1.97
(**2**)	$HL = L^- + H^+$	2	8.49[b]	−4.46	7.12

[a] Determinations by calorimetric titration. Uncertainties are given as standard deviations. [b] Values are approximate because (**2**) decomposes during the titration.



Ts = tosyl

Scheme 2. *Reagents and conditions:* i, tetraethylene glycol bis(toluene-*p*-sulphonate), Bu^{t}OK, Bu^{t}OH, dioxane, reflux, 24 h; ii, $C_8H_{17}Br$, Bu^{t}OK, Bu^{t}OH; iii, alumina column chromatography; $MeCO_2Et$.

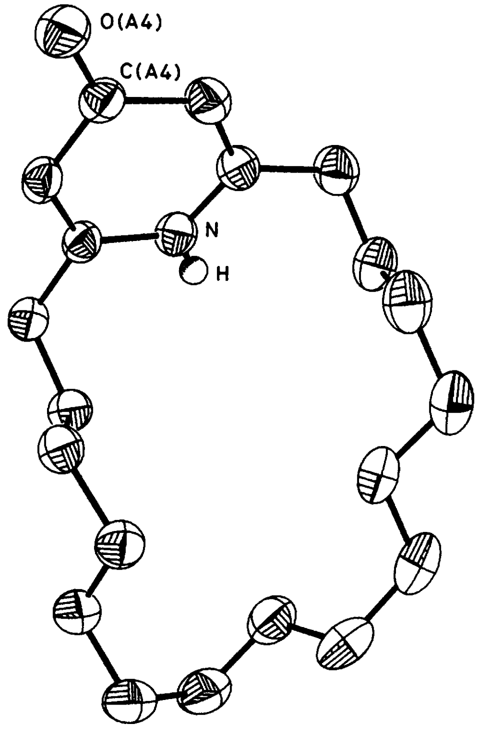


Figure 1. Computer drawing of (**1**). The hydrogen atoms bonded to the carbon atoms and to the water of hydration are omitted for clarity. *Crystal data:* $C_{15}H_{23}NO_6 \cdot H_2O$, monoclinic space group $P2_1/c$, a = 11.359(5), b = 7.628(2), c = 19.084(4) Å, β = 98.31(3)°, U = 1646.9 Å^3, Z = 4, D_c = 1.34 g cm^{-3}, μ(Cu-K_α) = 8.5 cm^{-1}. 2227 Non-zero independent reflections were measured (at room temperature) using a θ—2θ scan mode to a 2θ limit of 116° on a Nicolet R3 autodiffractometer with graphite monochromatic Cu-K_α radiation. The structure was solved using direct methods and refined using least-squares techniques. Non-hydrogen atoms were refined anisotropically. Positions for HN and for the hydrogen atoms of the water of hydration were obtained from difference maps and these atoms were refined isotropically. Locations for the remainder of the hydrogen atoms were calculated based on molecular geometry. The final residual values are R = 0.051 and R_w = 0.059. The weights were based on counting statistics.

Macrocycle (**1**) was prepared as shown in Scheme 1. The key intermediate (**8**)† was prepared in a good yield from chelidamic acid (**5**) as shown. The cyclization reaction of (**8**) and tetraethylene glycol bis(toluene-*p*-sulphonate) gave complex (**9**) in a 43% yield. Complex (**9**) was treated with acidified methanol to give (**1**)† in an overall yield of 26%, m.p. 104—105 °C. Compound (**2**) was prepared by first treating the dimethyl ester (**7**) with tetraethylene glycol and a trace of caesium methoxide in the presence of molecular sieve.[3] The tetrahydropyranyl (THP) blocking group was then removed in acidified methanol to give an overall 35% yield of (**2**),† m.p. 142—143 °C.

Compound (**2**) formed a stable complex with benzylamine, m.p. 180.5—181.5 °C. A similar attempt to form a complex of (**1**) with benzylamine was not successful. Both (**1**) and (**2**) formed stable complexes with benzylammonium perchlorate (m.p. 189.5—192 °C and m.p. 206—207 °C, respectively) as has been observed previously for these types of ligands.[4] Compound (**1**) was treated with octyl bromide in base to give compound (**3**)† as a liquid in a 90% yield (Scheme 2). We have also attached compound (**1**) to poly(vinylbenzyl chloride) by the same technique. An authentic sample of (**3**) was also prepared by the cyclization reaction of (**10**), prepared by reduction of the corresponding dicarboxylate,[4] and tetraethylene glycol bis(toluene-*p*-sulphonate) followed by column chromatography on alumina (Scheme 2). Diester compound (**4**)[5] was found to be a superior transport agent for Ag^+ across a chloroform membrane.[5] We believe that (**3**) will also be an

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† All new compounds gave satisfactory combustion analyses and i.r. and n.m.r. spectra and compounds (**1**) and (**2**) had the correct molecular weights.

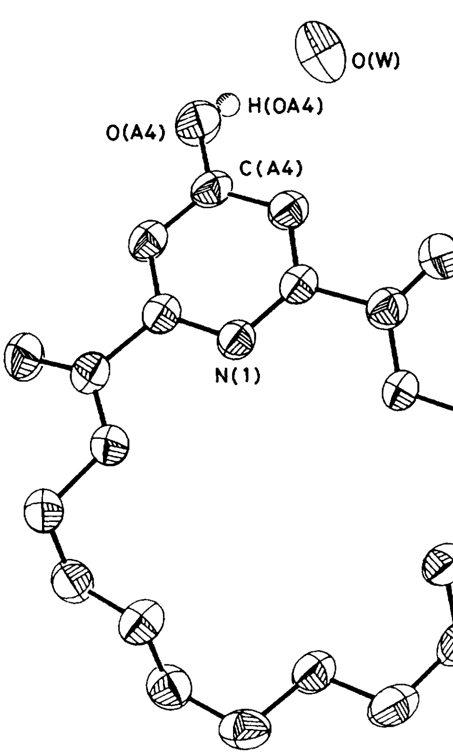

Figure 2. Computer drawing of (**2**). The hydrogen atoms with the exception of the hydrogen of the OH group of the pyridine moiety have been omitted. *Crystal data:* $C_{15}H_{19}NO_8 \cdot H_2O$, monoclinic space group *C2/c*, a = 20.673(5), b = 8.279(3), c = 20.895(7) Å, β = 101.13(2)°, Z = 8, D_c = 1.36 g cm^{-3}, μ(Cu-K_α) = 9.8 cm^{-1}. 2390 Non-zero independent reflections were measured using the same experimental conditions as for (**1**). The structure was solved and refined in the same manner as for (**1**). Non-hydrogen atoms were refined anisotropically. Positions for H(OA4) and the hydrogen atoms of the water of hydration were obtained from difference maps. Locations for the remainder of the hydrogen atoms were calculated as for (**1**). The resulting R value was 0.052. Unit weights were used in the refinement.

excellent ligand for the transport of cations and it is more stable than diester (**4**).

Values of pK_n, ΔH_n, and $T\Delta S_n$ are given in Table 1 for proton ionization from the H_2L^+ forms of (**1**) and (**2**). The pK_1 and pK_2 values for proton ionization from (**1**), 3.10 and 10.98, are similar to those for 4-hydroxypyridine, 3.27 and 11.09.[6] The corresponding ΔH_1 (0.99 kcal mol^{-1}) and $T\Delta S_1$ (−3.24 kcal mol^{-1})‡ values for (**1**) are also similar to those for 4-hydroxypyridine (1.49 and −2.9, respectively).[6] This similarity of pK and ΔH values indicates that compound (**1**) contains the 4-pyridone structure as is the case for the parent 4-hydroxypyridine.[7] The X-ray structure determination for (**1**) (discussed below) confirms the 4-pyridone structure. Even more interesting is the indication that compound (**2**) contains the 4-hydroxypyridine unit. Evidence for this structure is seen in the pK_1 and pK_2 values for (**2**) (Table 1) which are quite different from those for (**1**). The 4-hydroxypyridine structure is confirmed for the solid state by an X-ray structure determination for (**2**) which shows the 4-hydroxypyridine unit.

An X-ray§ structural study of the hydrate of (**1**) shows that the compound exists in the solid state as the 4-pyridone with the hydrogen atom on the pyridine nitrogen. A computer drawing of the molecule is shown in Figure 1.[8] The hydrogen on the pyridine N is evident in the difference map. Other supporting evidence for the pyridone form is the C–O distance of 1.261(3) Å which is in the range of C–O double bonds (1.23—1.26 Å).[9] The water of hydration is outside the cavity and forms a hydrogen bond with the carbonyl oxygen. An X-ray§ structural study of the hydrate of (**2**) shows that the compound exists in the solid state as the 4-hydroxypyridine. A computer drawing of the structure is given in Figure 2. The hydrogen atom H(OA4) was located in the difference map and was involved in a hydrogen bond with the oxygen atom of the water of hydration O(W), the H(OA4) · · ·O(W) interatomic distance being 2.578 Å. The C–O bond distance, 1.341(3) Å, also supports the presence of a single C–O bond. This C–O distance agrees well with that, 1.351(3) Å, found in a study of a compound similar to (**2**), but with H(OA4) replaced by a methyl group.[10]

The increased stability of crown (**1**) over diester crown (**2**) makes (**1**) an important intermediate for the synthesis of new crown systems such as the lipophilic ligand (**3**), which could be useful in carrier-mediated cation transport investigations. In addition, the reactive 4-OH group of (**1**) provides the possibility of attachment onto solid membranes.

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References

1 Y. Nakatsuji, T. Mori, and M. Okahara, *Tetrahedron Lett.*, 1984, **25**, 2171.
2 I. Ikeda, H. Emura, and M. Okahara, *Synthesis*, 1984, 73, and the references cited therein.
3 J. S. Bradshaw, B. A. Jones, R. B. Nielsen, N. O. Spencer, and P. K. Thompson, *J. Heterocycl. Chem.*, 1983, **20**, 957.
4 R. M. Izatt, J. D. Lamb, R. E. Asay, G. E. Maas, J. S. Bradshaw, J. J. Christensen, and S. S. Moore, *J. Am. Chem. Soc.*, 1977, **99**, 6134; J. D. Lamb, R. M.Izatt, C. S. Swain, and J. J. Christensen, *ibid.*, 1980, **102**, 475; J. S. Bradshaw, G. E. Maas, J. D. Lamb, R. M. Izatt, and J. J. Christensen, *ibid.*, p. 467; H. Tsukube, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 3882; J. D. Lamb, R. M. Izatt, C. S. Swain, J. S. Bradshaw, and J. J. Christensen, *J. Am. Chem. Soc.*, 1980, **102**, 479; J. S. Bradshaw, N. O. Spencer, G. R. Hansen, R. M. Izatt, and J. J. Christensen, *J. Heterocycl. Chem.*, 1983, **20**, 353.
5 R. M. Izatt, D. V. Dearden, P. R. Brown, J. S. Brashaw, J. D. Lamb, and J. J. Christensen, *J. Am. Chem. Soc.*, 1983, **105**, 1785.
6 J. J. Christensen, L. D. Hansen, and R. M. Izatt, 'Handbook of Proton Ionization Heats and Related Thermodynamic Quantities,' Wiley-Interscience, New York, 1976.
7 R. M. Acheson, 'An Introduction to the Chemistry of Heterocyclic Compounds,' Interscience, New York, 1967, pp. 218—222 for a discussion of the structure of 4-hydroxypyridine.
8 All computations and plotting were done using: G. M. Sheldrick, SHELXTL, 4th revision, 'An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data, University of Göttingen, Federal Republic of Germany, 1983.
9 'International Tables for X-ray Crystallography,' ed. K. Lonsdale, Birmingham, Kynoch Press, 1968, vol. III, 2nd edn., p. 276.
10 N. K. Dalley and B. E. Wilson, unpublished data.

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‡ 1 cal = 4.184 J.

§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.