

Basicity and Structure of 2,6-Pyrido-crown Ethers; the Effect of Ringsize, Solvent Interactions, and Hydrogen Bonding

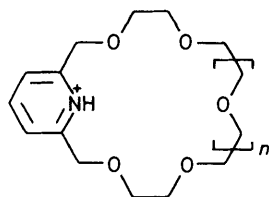
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The acidity of 2,6-pyridinium-crown ethers (**1**) varies with the ringsize [pK_a 4.88 (15-membered ring), 4.95 (18-), 4.16 (21-), 3.95 (24-), 3.70 (27-), 3.53 (30-), 3.36 (33-); H₂O, 25.0 °C]; X-ray analyses of the 2,6-pyrido-18-crown-6-H₂O-HClO₄ complex and the free 2,6-pyrido-18-crown-6 point to specific intra-annular hydration.

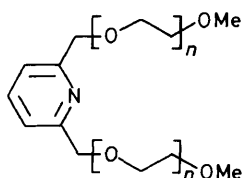
Proton transfer from host to guest in complexes of macrocyclic polyethers with organic molecules has not been considered in depth as a contribution to the stabilization of such complexes. [Cram and co-workers have reported proton transfer from 2,2'-bis(carboxymethoxymethyl)-1,1'-binaphthyl crown ethers to L-valine¹ and a crystalline complex of 2'-carboxy-1',3'-xylyl-18-crown-5 and t-butylamine.²] Earlier studies by our group have revealed that complexes of crown ethers with *neutral* molecules are thermodynamically far less stable than complexes with charged molecules.³ In relation to our work on the selective complexation of urea by a synthetic macrocyclic receptor molecule,⁴ we are currently studying the possibility of using proton transfer in complexation reactions. Previously we have shown that urea (pK_a 0.1, H₂O, 25 °C) can be protonated by strong inorganic acids and subsequently complexed by macrocyclic polyethers.⁵ Proton transfer from the macrocyclic ligand by an intra-annular proton donating group may result in an energetically more favourable host-guest complex. Only a few crown ethers with intra-annular proton donors^{2,6-8} have been reported, but in these macrocycles part of the cavity is occupied by the substituent. In protonated 2,6-pyrido-crown ethers⁹ (**1**) the whole cavity is available for complexation.

In this communication we report a study on the acidity of the pyrido moiety as a function of the number of ring atoms in the macrocyclic polyether. pK_a -Determinations were carried out in nitrogen-flushed H₂O, 25.0 °C, with 0.1 M HCl as titrant, by means of an on-line potentiometric titration device.¹⁰ Activities were used throughout the calculations for the determination of the pK_a -values with an iterative procedure based on the Newton-Raphson algorithm.



(1) ($n = 0-6$)

(4) = (1; $n = 1$) · H₂O · HClO₄



(2) ($n = 0$)

(3) ($n = 1$)

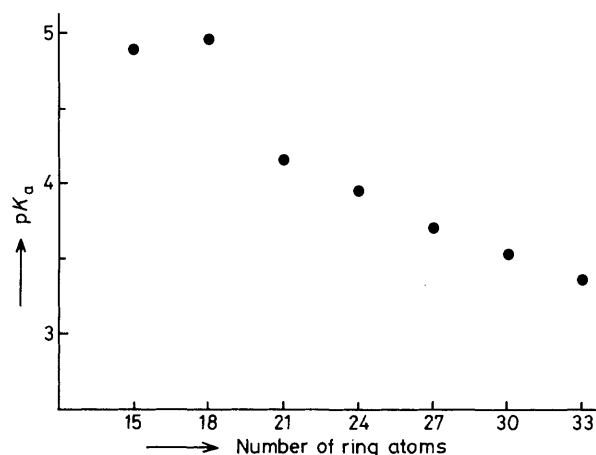


Figure 1. pK_a 's (± 0.02) of protonated 2,6-pyrido-crown ethers (**1**) ($n = 0-6$) (H₂O, 25.0 °C).

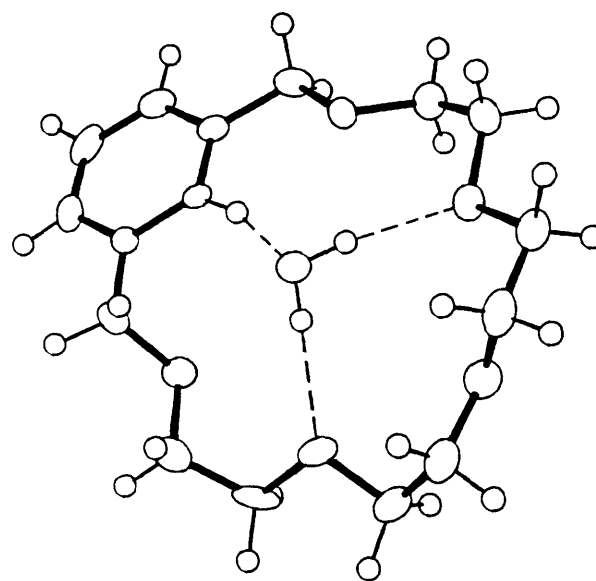


Figure 2. ORTEP¹⁴ view of 2,6-pyrido-18-crown-6-hydronium perchlorate (**4**). Crystal data: C₁₅H₂₆O₁₀NCl, monoclinic, space group $P2_1/n$, $a = 19.638(9)$, $b = 11.858(11)$, $c = 8.134(3)$ Å, $\beta = 95.05(2)^\circ$, $U = 1887$ Å³, $Z = 4$, $D_c = 1.468$ g cm⁻³, $\mu(\text{Mo-K}\alpha) = 2.1$ cm⁻¹. 3316 Reflections were measured (at 168 K) using the $\omega-2\theta$ scan mode ($3 < \theta < 25^\circ$) on a Philips PW1100 diffractometer with graphite-monochromated Mo-K α radiation. 2446 Reflections with $I > \sigma(I)$ (from counting statistics) were used for the solution by direct methods.¹⁵ All hydrogen atoms were located in a difference Fourier map. The structure was refined by least-squares methods¹⁶ to a final weighted R -factor of 5.5% (349 parameters refined: scale factor, isotropic extinction parameter, positional parameters, anisotropic thermal parameters for non-H atoms, isotropic for H).

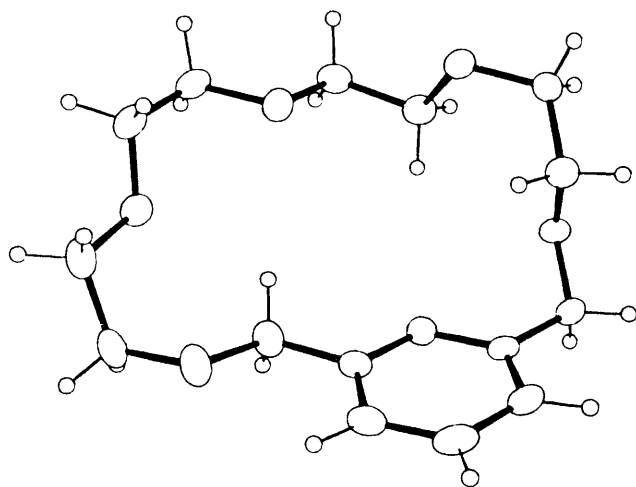


Figure 3. ORTEP¹⁴ view of 2,6-pyrido-18-crown-6 (**1**; $n = 1$). *Crystal data:* $C_{15}H_{23}O_5N$, monoclinic, space group $P2_1/n$, $a = 10.483(1)$, $b = 16.683(2)$, $c = 9.847(1)$ Å, $\beta = 117.32(2)^\circ$, $U = 1529$ Å³, $Z = 4$, $D_c = 1.295$ g cm⁻³, $\mu(\text{Mo-K}\alpha) = 0.9$ cm⁻¹. 2843 Reflections were measured (at 166 K) as for (**4**) ($4 < \theta < 25^\circ$). 2439 Reflections with $I > \sigma(I)$ (from counting statistics) were used for the solution by direct methods.¹⁵ All hydrogen atoms were located in a difference Fourier map. The structure was refined as before (see Figure 2 caption) to a final weighted R -factor of 3.5% (283 parameters refined).

For comparison the open-chain compounds (**2**) and (**3**) were prepared and the pK_a -values of the conjugate acids were found to be 3.36[†] and 3.53 respectively. Substituent effects cannot fully account for the enhanced acidity of (**2**) and (**3**) when compared with 2-(methoxymethyl)pyridine (pK_a 4.40)¹² and pyridine (pK_a 5.23). This may be attributed to steric hindrance of solvation of the pyridinium moiety by the two alkoxyethyl groups in the 2- and 6-positions of (**2**) and (**3**).

The macrocyclic effect on the pK_a -values in the pyridinium crown ethers (**1**) (Figure 1) causes a gradual increase of the acidity with increasing ring size, the pK_a of the 33-membered ring being close to that of the protonated open-chain pyridine derivative (**2**). The increase in basicity of the pyridine function with decreasing ring size may be explained in terms of a favourable solvation of the pyridinium-ion by additional co-ordination of the solvent molecules,¹³ which are further stabilized by the macroring oxygen atoms.

The relatively high basicity of the 18-membered pyrido-crown ether points to a unique highly structured water complex. This assumption was supported by the isolation of a crystalline 2,6-pyrido-18-crown-6·H₂O·HClO₄ complex (**4**) when an aqueous solution of 2,6-pyrido-18-crown-6 was treated with 20% HClO₄; crystallization from ethanol-water gave colourless crystals (m.p. 86–88 °C)[‡] in a yield of 53%. *X*-Ray analysis (Figure 2) revealed the structure of the complex. §¶ By linear interpolation from the pK_a data for part of the series of pyridinium macrocycles ($n = 2$ –6) a calculated value of 4.35 is obtained for the 18-membered pyrido-crown ether. This means that the additional stabilization of the protonated form in the H₂O complex corresponds to 0.6 pK_a

[†] The reported value of 4.9 (ref. 11) could not be reproduced.

[‡] Satisfactory elemental analysis was obtained.

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

¶ The complex shows some resemblance to the mono-aza-18-crown-6·H₂O·HCl complex (ref. 17).

units (-3.4 kJ mol⁻¹). Consequently the association constant of (**1**; $n = 1$) with H₂O can be calculated as 4 dm³ mol⁻¹. Although some crystalline H₂O complexes have been reported^{18–20} so far no thermodynamic data are available.

Corey–Pauling–Koltun model studies make it clear that the slightly enhanced basicity of the 15-membered cycle may be attributed to intra-annular hydrogen bonding of the protonated species.

Finally we have compared the structure of the complex with the free macrocycle. *X*-Ray analysis of (**1**; $n = 1$) (Figure 3) shows a conformation in which the cavity is filled by two hydrogen atoms; a similar phenomenon has been reported for 18-crown-6.²¹ Although the conformations depicted in Figures 2 and 3 are different, the nitrogen atoms in both structures point into the cavity. In the case of the free macrocycle 2,6-pyrido-24-crown-8 and the protonated form (**1**; $n = 4$), it has been shown by *X*-ray crystallography that the cavities are filled with CH-groups of the aromatic rings, the nitrogen atoms pointing outwards.⁹ Assuming that in solution these conformations with outward pointing nitrogen atoms also occur, the similarity in pK_a of open-chain compounds and the larger rings can be rationalized.

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