Binding of Ammonia and Some Amines to Crown Ethers Bearing an Intra-annular Phenolic Group

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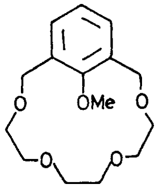
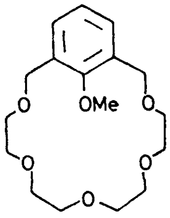
Summary The chemical behaviour of the crown-ether phenols (**3**)—(**6**) reveals that the phenolic group is strongly influenced by the encircling oxygen atoms of the crown, permitting the isolation of crown-stabilised ammonium phenoxides.

THE symmetrical substituted crown-ether phenols (**3**)—(**6**) were synthesised and their reactions with bases were studied to determine the influence of the proximate oxygen atoms of the crown on the chemical behaviour of an intra-annular phenolic group; conversely, information on how the ability of a crown ether to bond metal and ammonium ions is influenced by a strategically placed phenolic or phenoxide group was also sought. Phenolic groups play an important function in the structuring of some natural polyoxygenated ionophores capable of binding metal ions, *e.g.*, as in the barium salt of the antibiotic X-537A.[1] Crown-ether phenols of the type (**3**)—(**6**) have not been reported previously. Three diphenols in the binaphthyl crown series[2] have been prepared; in each case the substituent inhibits binding of alkali metal and ammonium ions, an effect attributed to the existence of strong intramolecular hydrogen bonding between the phenolic group and transannular oxygen atoms.[2] Other inward-pointing substituents attached to the 2-position of a 1,3-xylyl unit whose effect on the binding properties of crown ethers has been studied include carboxy,[3] methoxycarbonyl,[3] and methoxy.[2,4] We have found that the chemical behaviour of the phenolic group is markedly influenced by the encircling oxygen atoms of the crown and now report the first crown-stabilised ammonium phenoxides.

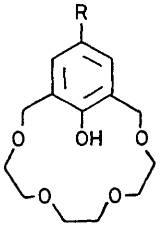
Condensation of 2,6-bis(bromomethyl)anisole[5] with the appropriate polyethylene glycol in hot tetrahydrofuran containing sodium hydride produced the methoxy 15-crown (**1**) and the methoxy 18-crown (**2**) in 45 and 58% yields, respectively, after distillation. Differences in intramolecular crowding near the centre of the macro-ring were apparent from the ^{1}H n.m.r. spectra of (**1**) and (**2**): the benzylic protons of the larger ring appeared as a singlet but were an AB quartet in the smaller ring.† Exposure of (**1**) and (**2**) to anhydrous lithium iodide‡ in dry pyridine at 100 °C for 10 h caused demethylation, producing, after acidification, the crystalline phenols (**3**), m.p. 66·0—66·5 °C, and (**5**), m.p. 48—49 °C in >90% yield. These demethylations were clearly subject to intramolecular crown-ether catalysis; neither anisole nor 2,6-dimethylanisole furnished detectable amounts of the lithium phenoxide when similarly treated.‡ The benzylic protons in both (**3**) and (**5**) appeared as singlets in the n.m.r. spectra. Nitration of (**3**) and (**5**) using dil. HNO_3 containing $NaNO_2$ at 20 °C produced the *p*-nitro derivatives (**4**), m.p. 105—106 °C, and (**6**), m.p. 91·0—91·5 °C. All four phenols exhibited strong intramolecular hydrogen bonding.



(1)



(2)



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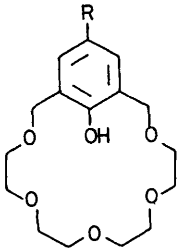
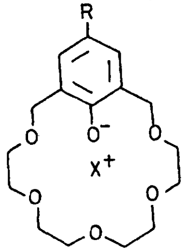
(4) R = NO_2



(5) R = H
(6) R = NO_2



(7) R = H
(8) R = NO_2

Treatment of a methanolic solution of the larger phenol (**5**) with dry ammonia gas caused complete conversion, judged by u.v. spectroscopy, into the ammonium phenoxide (**7**), λ_{max} 302 nm. Neither phenol nor 2,6-dimethylphenol gave an ammonium phenoxide detectable by u.v. spectroscopy when similarly treated. This contrasting behaviour is not due to pK_a differences [measured spectrophotometrically in water at 20 °C, phenols (**3**) and (**5**) had pK_a values of 10·8 and 10·6, respectively, compared with 10·7 for 2,6-dimethylphenol (lit.,[6] 10·7)] but can be interpreted as resulting from enhanced stabilization of phenoxide (**7**) ($X{=}NH_4$) through solvation of $^+NH_4$ by the crown oxygen atoms. However, the crown size is also important: when the smaller phenol (**3**) was exposed to ammonia in methanol only slight (*ca.* 5%) conversion into the phenoxide was observed. The ring size effect was also apparent from comparison of the ability of the methoxy and phenol crowns to extract ammonium picrate from water into chloroform, the 18-crown being more effective than the 15-crown with the methoxy compounds being much better than the phenols.§ Changing the solvent from methanol to carbon tetrachloride

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† For a detailed discussion of the conformational behaviour of related *meta*-cyclophanes, see ref. 5.

‡ This demethylation procedure is due to I. T. Harrison, *Chem. Comm.*, 1969, 616, who found that higher temperatures were required than those used here for (**1**) and (**2**).

§ In the binaphthyl series the methoxy group is also more effective than the phenolic group in binding picrate salts, see ref. 2.

in the reaction of the 18-crown phenol with ammonia caused precipitation of the crystalline phenoxide (**7**) ($X=NH_4$) which, upon isolation, slowly reverted to its components. Unstable crystalline phenoxides were also obtained with the 18-crown phenol and methylamine and t-butylamine. The Li^+, Na^+, and K^+ salts of (**5**) were soluble in both water and chloroform. The *p*-nitrophenol (**6**), $pK_a = 6{\cdot}6$, gave stable crystalline adducts with sodium, ammonia, t-butylamine, and α-methylbenzylamine. The sodium salt of (**6**) moved readily on a t.l.c. plate and its mass spectrum exhibited an intense $M^+ - NaNO_3$ peak at *m/e* 294. Using a simple U-tube arrangement it was possible to show that *p*-nitrophenol (**6**) was effective in transporting Na^+ ions, from aqueous NaOH, through a chloroform membrane.

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